DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

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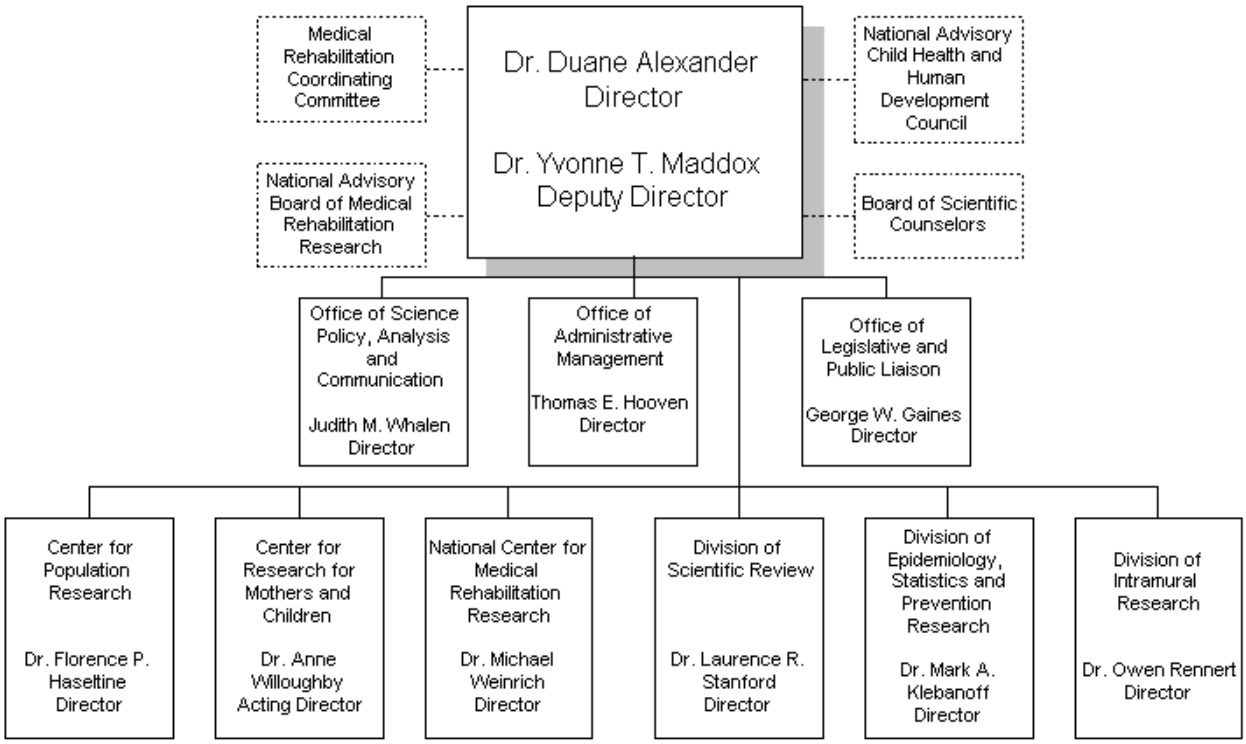

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

For carrying out Section 301 and title IV of the Public Health Service Act with respect to child health and human development, [$976,455,000] *$1,096,650,000*.

[Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act as enacted by the Omnibus Consolidated and Emergency Supplemental Appropriations Act for Fiscal Year 2001 (P.L. 106-554)]

National Institutes of Health

National Institute of Child Health and Human Development

Amounts Available for Obligation 1/

Source of Funding	FY 2000 Actual	FY 2001 Estimate	FY 2002 Estimate
Appropriation	$862,884,000	$976,455,000	$1,096,650,000
Enacted Rescission	(4,593,000)	(486,000)	---
Subtotal, Adjusted Appropriation	858,291,000	975,969,000	1,096,650,000
Real transfer to:			
Other NIH Institutes through the NIH Director's one-percent transfer authority	(720,000)	---	---
Other HHS Agencies through Secretary's one-percent transfer authority	(179,000)	---	---
Real transfer to HHS for the Office of Human Research Protection	---	(203,000)	---
Comparative transfer from:			
Office of the Director for the Academic Research Enhancement Award program	767,000	800,000	---
Office of the Director for the Extramural Associates Program	2,234,000	2,340,000	---
Other NIH Institutes as a result of a change in assessment formula for Central Services funding	967,000	---	---
Subtotal, adjusted budget authority	861,360,000	978,906,000	1,096,650,000
Unobligated balance lapsing	(38,000)	---	---
Total obligations	861,322,000	978,906,000	1,096,650,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: FY 2000 - $11,815,000
FY 2001 - $16,000,000 FY 2002 - $16,000,000
Excludes $154,582 in FY 2000 and $156,000 in FY 2001 for royalties.

Justification

National Institute of Child Health and Human Development (NICHD)

Authorizing Legislation: Section 301 and title IV of the Public Health Service Act, as amended. Reauthorizing legislation will be submitted.

Budget Authority

FY 2000 Actual		FY 2001 Estimate		FY 2002 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
542	$861,360,000	559	$978,906,000	580	$1,096,650,000	21	$117,744,000

INTRODUCTION

This document provides justification for the Fiscal Year (FY) 2002 activities of the National Institute of Child Health and Human Development, including HIV/AIDS activities. A more detailed description of NIH wide FY 2002 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research" (OAR).

Since its inception, the NICHD has dedicated its research to understanding the dynamic biological, behavioral, and social processes that dictate physical, emotional, and cognitive growth. The focus of NICHD research starts at the beginning of the developmental process, from before conception through the transitions of infancy, childhood, and adolescence, which set the foundation for conditions, diseases, and behaviors that last a lifetime. Thus, the Institute's broad mission encompasses research on infant mortality; prevention of birth defects, including genetic diseases; learning disabilities; the development and evaluation of contraceptives and infertility treatments; mental retardation and developmental disabilities; developmental and reproductive biology; vaccine development; fetal medicine; demographic and behavioral sciences; and the enhancement or restoration of function in individuals with a physical disability.

Despite the wide diversity of the areas of science that we actively investigate, major progress has been achieved as the Institute helps scientists to better understand the complex interplay of processes that transform cells into healthy functioning individuals, free of disease and disabilities. When the goal is not achieved, the NICHD mission is to understand why and to develop remedies to ensure the healthy functioning of all infants, children, youth, and families.

On the other hand, as we succeed, we will solve many of the world's most significant problems: ending unchecked population growth, minimizing mortality and morbidity of children, establishing a healthy physical and social environment, maximizing learning ability, preventing adult disease that originates prenatally or in childhood, preventing violence by developing

healthy behavioral and social skills, and ultimately eliminating health disparities among various populations.

In addition, the success of our research promises economic as well as social benefits. For example, the three conditions with the highest hospital charges are infant respiratory distress syndrome (average length of stay 24.6 days, at an average cost of $68,000), spinal cord injury (15.9 days at $53,000), and prematurity and low birthweight (21.7 days at $50,000). All three are major targets of NICHD research.[1]

However, success in achieving our goals comes slowly, and often with one small advance at a time. Each advance has its own story and provides a basis for the next discovery. For the NICHD, a number of compelling research discoveries have emerged:

- NICHD intramural scientists have field-tested a new conjugate vaccine to prevent typhoid fever in children living in developing countries. Even in conditions of heavy exposure to the disease, the vaccine demonstrated 91 percent protective efficacy--a remarkable achievement. Trials are now underway to assess whether the vaccine can also be protective when given to infants along with their routine immunizations.

- For more than two decades, a debate has raged over whether epidural analgesia given to pregnant women to ease the pain of labor slows down the labor process and increases the likelihood of delivery by cesarean section. In one simple study, NICHD scientists have put the issue to rest. Examination of data from a hospital where use of epidurals went from almost zero to more than 70 percent of deliveries in one year revealed no significant change in the duration of labor, and no increase in the cesarean delivery rate. Women wishing to reduce the pain of childbirth may now freely choose epidural analgesia without fearing that it will increase their chance of cesarean delivery.

- Recently, an NICHD grantee received a patent for new synthetic hormones that are considerably more potent than the naturally occurring male hormone, testosterone. These synthetic compounds have been tested in animal models and, if found to be safe, will be evaluated clinically. This patent is the first step towards a male contraceptive that could provide men with one of their first new reproductive options in many years.

The NICHD is proud of these and our many other achievements, and plans to build upon them by implementing new strategic research agendas and major research initiatives. These should provide the science to better treat and prevent a wide range of conditions, through the conscientious design of research, and through the acts of scientists working together with individuals and communities.

[1] Agency for Healthcare Research and Quality, "Co-morbidities/Insurance/Discharges--Hospitalization in the United States, 1997: http:// www.ahrq.gov/data/hcup/factbld1/fctbk3.htm.

How an Air Pollutant Became a Life Saving Treatment for Newborn Infants

Blue baby. At first glance, the term seems an innocent description of a character in a children's storybook. In reality, the term refers to newborns whose lungs cannot absorb enough oxygen for the babies to live. Recently, however, NICHD-sponsored researchers pioneered a new treatment for the condition known as hypoxic respiratory failure. In a story typical of the twisting path of scientific discovery, the new treatment was developed from basic research on nitric oxide, a gas that is a major component of polluted air.

The story began in 1987, when researchers discovered that the gas caused the muscles controlling the lining of the heart and blood vessels to relax. At first, the scientific community was skeptical that a gas that is an air pollutant could perform such an important function. Later, research confirmed that nitric oxide was central to many biological functions. Poisonous in large quantities, nitric oxide nonetheless is produced in tiny amounts throughout the body.

In addition to relaxing blood vessels, scientists later found that the gas could help brain cells communicate with each other and immune cells kill disease-causing organisms, as well as assist the body's response to burns. From these basic discoveries, researchers are developing a number of treatments, including ones for high blood pressure, stroke, heart failure, complications of diabetes, and impotence.

The unique ability of nitric oxide to relax blood vessels, however, also intrigued researchers studying hypoxic respiratory failure. For reasons scientists do not fully understand, 2 out of every 1000 full-term infants suffer from this condition, which is actually a form of high blood pressure of the lungs. Blood vessels that would normally soak up oxygen-rich blood from the lungs remain tightly constricted so that too little oxygen is absorbed to keep the baby alive.

Most commonly, physicians first treat these infants by putting them on a ventilator to deliver 100 percent oxygen into the infants' lungs. If this is unsuccessful, physicians then turn to a procedure called extracorporeal membrane oxygenation (ECMO), which takes blood from a vein entering the heart and adds oxygen to it, before returning it to the body. ECMO, however, carries with it a 20 percent risk of permanent brain damage, and for every 100 infants who receive ECMO therapy, only 82 survive.

Now, in the first conclusive trial of its kind, researchers from the NICHD Neonatal Research Network have shown that using inhaled nitric oxide is an effective therapy for hypoxic respiratory failure in full-term infants who fail to respond to maximal conventional therapy, including100 percent oxygen. The study enrolled more than 200 infants suffering from hypoxic respiratory failure. Of those who received inhaled nitric oxide, about 46 percent needed ECMO therapy or died. In contrast, 64 percent of infants who only received the conventional therapy of 100 percent oxygen were referred for ECMO therapy or had died. (The number of deaths among the two groups did not differ significantly, 14 percent for the nitric oxide group and 17 percent for the control group.)

When the infants were tested between 18 and 24 months of age, there was no increase in signs of damage to the brain or nervous system in the babies who received nitric oxide compared to those who received the standard treatment. Based on these studies, inhaled nitric oxide therapy for newborns suffering from hypoxic respiratory failure was approved by the Food and Drug Administration as an acceptable medical treatment. The NICHD Neonatal Research Network is now conducting a trial to see if inhaled nitric oxide can also benefit premature infants with severe lung disease.

NICHD Research:
Addressing Critical Public Health Issues For Children, Women and Families

Saving Precious Lives: Improving Key Measures of Infant Health and Well-Being

Infant mortality and morbidity rates not only measure the loss of new lives, they also indicate the overall health of a nation. The NICHD supports a unique portfolio of research aimed at

understanding the causes and biological mechanisms of infant deaths and illnesses occurring during the first year of life. Since the Institute was established, the U.S. infant mortality rate has decreased 70 percent[2], due in large part to research that has led to new ways to treat and prevent respiratory distress syndrome, care for premature infants, and prevent birth defects and Sudden Infant Death Syndrome (SIDS). Future research offers hope of further improving health outcomes for all newborns.

Marking Time: Pregnancy-Related Protein Predicts Preterm Births– Preterm birth is the leading cause of infant mortality and morbidity among African-American infants in the U.S. and the second leading cause of infant mortality among all races.[3] The long-term outlook faced by an infant that is born too soon can be bleak: increased risk of illness, disability, and early death. In the search for a biological marker that can reliably predict pre-term births, NICHD-sponsored researchers screened more than 13,000 pregnant women. They discovered that a markedly increased level of the protein fetal fibronectin (FFN), found in maternal vaginal secretions, correlates with an increased likelihood of premature delivery. FFN appears to help the embryo attach to the uterine wall and the placenta develop. The researchers noted that abnormally high levels of FFN found between the 13th and 28th weeks of pregnancy indicate a four-fold increase in the risk of premature birth. Moreover, the study showed that groups already known to have a statistically higher likelihood of preterm delivery--African-Americans, women with vaginal infections, and women who have already given birth to at least two live children--had higher proportions of individuals with elevated FFN levels than did the general population. This discovery offers clinicians a powerful tool for predicting preterm births and improving the care of those at high risk.

Antibiotic Therapy for a Common Vaginal Infection Increases Preterm Births -- Trichomoniasis, a common genital tract infection in men and women, is another infectious organism that has been linked to preterm births. Because most women do not display overt symptoms of infection, some experts have argued that all women should be screened when they become pregnant and then treated for the infection, if necessary. Only one antibiotic, metronidazole, is effective against trichomoniasis. To test the value of this treatment in reducing the incidence of preterm births, NICHD scientists recently conducted a controlled trial among asymptomatic pregnant women with trichomoniasis, half of whom received metronidazole and half of whom received a placebo. Contrary to expectations, researchers found that metronidazole therapy actually *increased* the incidence of premature delivery. By raising serious concerns about the wisdom of prescribing antibiotics, especially metronidazole, to pregnant women, this study may indicate the need for clinicians to modify current clinical guidelines. However, further studies are required before scientists can definitively establish the actual level of risk that antibiotic therapies may pose for pregnant women.

Brain Abnormalities in SIDS Infants: Uncovering Pathways to Sudden Infant Death -- The dramatic 38-percent reduction in SIDS deaths that has occurred since the start of the NICHD

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[2]National Center for Health Statistics. Trends in Health and Aging. Table 22. Infant mortality rates, fetal mortality rates, and perinatal mortality rates, according to race: United States, selected years, 1950-97. http://www.cdc.gov/nchs/products/pubs/pubd/hus/tables/99hus022.pdf

[3]National Center for Health Statistics: http://www.cdc.gov/nchs/about/major/lbid/t1causes.htm

Back to Sleep campaign has played a major role in reducing the U.S. infant mortality rate.[4] To fully eliminate the syndrome, however, scientists must continue to seek out the neurological basis for SIDS. Building on earlier findings of brain abnormalities in babies who died of SIDS, scientists have now discovered that such defects affect more areas of the brain than previously thought. The research revealed flaws in the way a large network of brain cells use serotonin, an essential chemical involved in communication between nerve cells. The neural network affected by this abnormality may play a role in controlling breathing, heartbeat, temperature, and waking during sleep. Defects in this network could interfere with a baby's ability to awaken itself when he or she has trouble breathing, or becomes overheated while asleep. Future research in this area could clarify how this specific neural network develops and functions from fetal life through infancy, leading to new ways to screen newborns for the defective network and to better protect those with the defect. Ultimately, this research offers hope for preventing many of the nearly 3,000 deaths from SIDS that still occur each year.[5]

Choosing a Safe Sleep Position: Listening to the Doctor's Advice -- Despite the success of the *Back to Sleep* campaign, approximately one-fifth of babies are still placed to sleep on their stomachs, putting these infants at increased risk for SIDS. The latest results from the National Infant Sleep Position (NISP) Study provide insights into what motivates caregivers (i.e., parents, grandparents, day care providers) to heed advice about placing babies on their backs to sleep. The study found that physicians had the greatest influence on whether or not caregivers placed infants to sleep on their backs; however, 41 percent of those responding to the survey said that their physician had not made a recommendation on sleep position. Other sources of information that helped increase the rate of back sleeping included nurses, reading materials, and radio or television. The study also revealed that caregivers are more likely to place an infant to sleep on its stomach if they perceived that the baby was more comfortable or slept better in that position. These findings suggest new opportunities for expanding the success of the *Back to Sleep* campaign by targeting specific issues identified by the NISP Study, including the need for physicians to discuss the choice of infant sleep position with caregivers.

New Drug Interrupts Preterm Labor -- Several drugs have been developed to interrupt spontaneous preterm labor and reduce the possibility that premature contractions may reoccur. The effectiveness of these agents, however, is highly limited, and their use is associated with significant side effects. NICHD researchers recently conducted two trials involving more than 1500 at-risk pregnant women to assess the efficacy and safety of a highly innovative drug, Atosiban. Atosiban blocks the action of oxytocin, a maternal hormone that stimulates labor by initiating uterine contractions. In the first trial, which tested Atosiban's effectiveness in interrupting uterine contractions, researchers found that the drug could prolong pregnancy for up to seven days in women who had been pregnant for at least 28 weeks while causing no serious side effects. The second trial showed that Atosiban can be effectively used to prevent spontaneous labor from reoccurring, again without significant side effects. Although more trials are needed to provide definitive proof of Atosiban's safety and effectiveness, these results

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[4]Willinger M, Hoffman HJ, Wu K-T, Hou J-R, Kessler RC, Ward SL, Keens TG, and Corwin MJ: Factors associated with the transition to nonprone sleep positions of infants in the United States: The National Infant Sleep Position Study. JAMA 280:329-335, 1998.

[5]National Vital Statistics Reports, Vol. 48, No. 11.

suggest that the drug may be a viable alternative to the drugs currently available, and may help reduce the overall incidence of preterm delivery.

Why Fingers Aren't All Thumbs: New Insights Into Birth Defects -- Having fingers and toes of different sizes has allowed humans to master activities ranging from playing the violin to eating with chopsticks, yet why a pinkie becomes a pinkie and not another thumb has puzzled developmental biologists for decades. In both humans and animal model systems, hands and feet start off with webbing surrounding the digits, but as early development progresses, the cells that compose this webbing die off, leaving individual fingers and toes. While scientists had previously identified genes that control how the basic cartilage framework of early digits develops, they did not yet understand how exquisite differences develop between each finger in the hand, or each toe in the foot. A new study offers some surprising insights: NICHD-supported researchers have demonstrated that the mechanisms that "tell" digits what to become operate at much later stages of embryonic development. Furthermore, this molecular signal originates from the webbing surrounding the digits before it dies off. This signal, which is provided by molecules called bone morphogenetic proteins (BMP's), plays a pivotal role in establishing digit identity. Delineating the role of BMPs in the development of human hands and feet opens the door, not only to correcting congenital malformations of the hands and feet, but may enable researchers to regenerate digits after injury or loss.

Innovative Home Video Course Helps New Parents Improve Infant Health -- New parents often lack accurate, reliable information about their infant's healthcare needs and development during the first year of life. To bridge this critical information gap, scientists sponsored by an NICHD Small Business Innovation Research grant developed and tested "My Baby U." My Baby U is an innovative, research-based home video course designed to help new parents become more knowledgeable, observant, and responsive to their infants' cues. The researchers found that, not only did young mothers who viewed the video learn significantly more about infant health and development than did non-participating mothers, but they were also more actively involved in meeting their infants' health needs. Moreover, their infants experienced fewer severe illnesses and required far fewer medical services than did the infants of non-participating mothers. The findings suggest that, with proper education, parents can improve their understanding of their infants' needs and have a positive effect on their infants' health. More widespread use of such education programs may significantly improve health outcomes and help lower infant health care costs.

The Science Behind Learning: Helping Children Achieve Their Full Potential

The ability of students to think, learn, and communicate is a key to their success not only in school, but throughout life. New data, which show that events and experiences from conception onward have a critical influence on the developing brain, offers hope that changes in children's environments can help them overcome learning and developmental disabilities, regardless of socioeconomic status. NICHD-supported basic research is unraveling the complex ways in which genetics and other biological factors interact with the environment to influence how children learn. In addition, the Institute supports behavioral and applied research to help educators, physicians, and policymakers develop the most effective, scientifically based interventions for fostering early educational competence in our children.

Scientists Identify Gene Involved in Learning -- A crucial aspect of learning is the brain's capacity to alter connections (synapses) between nerve cells (neurons) in response to activity stimulated by behavior and experiences. This ability, called synaptic plasticity, allows the brain's complex network of one trillion neurons and 70 trillion connections to be fine-tuned throughout an individual's development and adulthood. By studying fruit flies, researchers have discovered that a protein coded by the gene *latheo (lat)* plays a central role in adult learning and synaptic plasticity. Researchers theorize that the *lat* gene becomes active when a specific experience such as learning stimulates neural activity. This activity, in turn, switches on various signaling pathways among specific neurons. Continued experience, or learning, can sufficiently activate these pathways to stimulate a growth process that ultimately changes synapses and is associated with long-term memory function. This research supports the theory that common genetic mechanisms are responsible for how nerve cells adapt as one matures, and for long-term memory formation. Understanding these mechanisms may eventually suggest new avenues for treating or modifying developmental learning disorders.

A Link Between Formula Additives and Children's Intelligence -- Nutrition is one of many non-genetic factors that can affect early brain development and influence a child's ability to learn. However, the question of whether specific nutrients found in human milk promote cognitive development has been controversial. For years, infant formulas available outside the United States have routinely contained two substances found in human breast milk and believed to play a role in the development of the nervous system. Now, scientists have provided strong evidence that adding these substances (docosohexaenoic acid [DHA] and arachidonic acid [AA]) to infant formula boosts intelligence. At 18 months, infants whose formula was supplemented with both DHA and AA scored significantly higher in tests measuring memory, problem-solving abilities, and language capabilities than infants who received only DHA or neither of the supplements. These findings are an important step in addressing the urgent public health issue of whether DHA and AA should be added to infant formula in this country. Additional studies are needed to determine the long-term safety and benefit of formulas containing these supplements.

Long-Term Effects of Iron-Deficiency Anemia in Infancy -- Iron is another nutrient that is important for early brain development and mental functioning. But approximately five percent of poor African American and Hispanic infants and toddlers, and specifically 18 percent of poor Mexican-American infants, have iron-deficiency anemia. Worldwide, 20 to 25 percent of all infants have the condition.[6] Some long-term effects of iron deficiency in infants have been revealed in a study conducted more than 10 years after infants were treated for this condition. Researchers found that a group of Costa Rican adolescents who had been tested and treated for severe chronic iron deficiency in infants, scored lower on measures of mental and motor function than did adolescents who had good iron status in infancy. In addition, more children who formerly had iron deficiency had repeated a grade, been referred for special services or tutoring, or exhibited problem behavior such as depression, anxiety, and attention deficits. The long-term

[6] DeMaeyer E, and Adiels-Tegman M: The prevalence of anaemia in the world. World Health Stat. Q. 38:302-316, 1985; Looker AC, Dallman P, Carroll MD, Gunter EW, and Johnson CL: Prevalence of iron deficiency in the United States. JAMA 277:973-976, 1997.

behavioral and developmental disadvantages revealed by this study highlight the importance of early screening and treatment for iron-deficiency anemia, particularly for minority infants, to ensure normal brain development.

Reading Behavior and Brain Function Can Be Improved in Older Children -- Children who have difficulty reading are at risk for failure in school, may lose their enthusiasm for learning, and often are unable to reach their full potential. Yet dyslexia, the inability to read due to poor recognition of word sounds, affects from 10 to 20 percent of children in the United States.[7] While previous studies have shown that dyslexia can often be prevented if identified early (before first grade), treating older children for this difficulty has been challenging. However, a recent study has demonstrated that reading disabilities in children between 10 and 13 years of age *can* indeed be corrected. Older children with severe dyslexia improved and maintained reading skills after an intensive 3-week reading and science workshop that taught them how to detect and manipulate sounds within speech units ("phonological processing"). In addition, non-invasive brain scans of the children, conducted both before and after treatment, showed that the children had changes in brain activity that were directly related to the improvements in reading and language. These findings suggest that the brain can adapt and possibly reorganize itself to aid in language-related learning, even as late as middle childhood.

Panel Provides Guidance on Effective Ways to Teach Reading -- Some children will learn to read with ease, whatever teaching method is used. But for an estimated 60 percent of our nation's children, learning to read is a formidable challenge.[8] Now, an independent National Reading Panel (NRP) supported by the NICHD has provided much-needed guidance on the most effective ways to teach children to read. Members of the congressionally mandated panel used rigorous scientific standards to review more than 100,000 reading research studies and to identify the most effective teaching approaches based on that evidence. The NRP concluded that instruction using a combination of methods is best for children. This includes teaching children to recognize and manipulate the sounds that make up words (phonemes), instructing children to use letter-sound combinations to read or spell words (phonics), and promoting children's ability to read fluently through guided oral exercises. Implementing these approaches in the nation's classrooms has the potential not only to enhance the well-being of our children and their families but also to improve the future literacy, global competitiveness, and economic prosperity of this country.

Variations in the HOXA1 Gene Linked to Autism -- Strong evidence now suggests that autism has a genetic basis. NICHD scientists have discovered a region on the human *HOXA1* gene that is associated with autism. The *HOXA1* gene is critical for neurological growth in the first few weeks after conception. Previous studies had shown that mice without *HOXA1* and a related gene *HOXB1* exhibited characteristics similar to autism. According to this new study of humans,

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[7] International Dyslexia Association. http://www.interdys.org/abcsofdyslexia/page4.asp

[8] Lyon GR: Overview of reading and literacy initiatives. Statement to the Committee on Labor and Human Resources, April 28, 1998. www.nichd.nih.gov/publications

certain codes in the *HOXA1* gene may play a role in making some families and individuals more susceptible to this disorder. Collectively, the earlier mouse studies and these latest findings on humans support the theory that autism arises from a disruption in early brain development. With this new knowledge, scientists can begin to focus specifically on the coding variation in the *HOXA1* gene and learn more about how this mutation leads to autism. Ultimately, this knowledge may help scientists to develop a method to diagnose autism much earlier or prevent its occurrence.

Widely Marketed Hormone Does Not Improve Autism -- The NICHD is supporting a series of clinical studies to investigate the validity of claims surrounding the use of the hormone secretin to treat autism. Results from the first study indicate that treatment with a synthetic version of secretin offers no more benefit for children with autism than does placebo treatment. Secretin, a hormone produced within the intestine, acts upon the pancreas to assist in digestion. In 1998, various media accounts described how a 3-year-old boy with autism and symptoms of digestive disorders improved dramatically within a week after being administered secretin. Based upon this and similar anecdotal reports, many parents sought out the treatment regimen. Since the drug was not readily available, sales of the hormone increased on the black market. At that time, no scientific evidence existed documenting the safety and effectiveness of these hormonal injections for children with autism. These initial findings strongly suggest that secretin *should not* be used to treat autism until final results of ongoing studies are known.

Infertility: Understanding the Causes and the Consequences

Helping couples who have difficulty conceiving requires understanding not only the intricacies of fertilization, but also the many biological factors involved in establishing and maintaining a healthy, full-term pregnancy. NICHD-sponsored research is increasing our knowledge of how embryonic cells grow after fertilization has occurred, how flawed biochemical interactions between mother and developing child may lead to miscarriage, and how genetic mutations may interrupt embryonic development. Moreover, despite the rapid increase in the number of sophisticated techniques to help couples overcome infertility, assisted reproductive technologies are not yet perfected. To understand the long-term effects of these procedures on human development, researchers are also developing animal models to examine the biological implications that such interventions may hold for future generations.

Researchers Discover New Gene Essential for Female Fertility -- After fertilization occurs, so-called "maternal-effect" genes control early cell division until the developing embryo's own genes become active. Scientists have now confirmed that a protein produced by a maternal-effect gene, appropriately named "*MATER*," must be present for fertilized eggs to develop beyond the two-cell stage in mice. The investigators bred genetically engineered female mice lacking *MATER* protein that ovulated normally but did not produce offspring. Further examination revealed that while fertilization took place in these mice, embryonic development abruptly stopped at the two-cell stage. Investigators are now working to identify a similar gene in humans. If found to be abnormal, the gene may reveal possible causes for unexplained cases of infertility in women who ovulate normally.

Preserving Fertility After Cancer Therapy -- Cancer treatments such as radiation and chemotherapy can greatly reduce the limited supply of eggs ("oocytes") a woman has available

for reproduction. Thus, young women who have successfully battled cancer are usually infertile, and subject to premature menopause and its related health problems. A new study by NICHD-funded researchers shows that it may be possible to protect the ovarian follicles that produce eggs. Researchers noticed that mice engineered to lack the "acid sphingomyelinase" gene had more new follicles than normal mice, and hypothesized that blocking this chemical could reduce the programmed death of follicles. Following chemotherapy, the follicles in normal mice were destroyed; however in mice engineered to lack the acid sphingomyelinase gene, the ovarian follicles survived chemotherapy. Similarly, when the ovaries were injected with S1P (a compound that counteracts sphingomyelinase) before radiation treatment, the follicles survived the treatment, whereas in mice injected with a control substance, the follicles "died." Because S1P is a small, injectable molecule, it is an excellent candidate to protect follicles in women being treated for cancer. Currently, women undergoing radiation or chemotherapy have very limited options to help to preserve their fertility. This important study provides a potential new way to preserve fertility and maintain normal "aging" of the reproductive organs for these women.

Scientists Uncover No Adverse Effects from Common In Vitro Fertilization Procedure -- Intracytoplasmic sperm injection (ICSI) has become the method of choice to help overcome male infertility and is widely used by infertility clinics around the world. The ICSI method allows clinicians to inject either mature or immature sperm directly into an oocyte, or egg cell. This technique bypasses many natural biological processes involved in fertilization and allows sperm from an infertile male, which could not enter into an egg under normal or *in vitro* conditions, to be simply injected into the egg's cytoplasm to initiate embryo development. After transfer to a uterus, the embryo can develop into live offspring. Researchers are particularly interested, however, in whether repeated use of the ICSI method, especially when immature sperm are used, will have serious consequences on the fertility and behavior of offspring. To gain preliminary answers, researchers performed the ICSI procedure in several generations of mice and found that they had no obvious developmental, behavioral, or reproductive abnormalities. However, it is important to note that *normal fertile mice* were used in this study, and further study is needed to understand the long-term implications of this procedure for humans. Nevertheless, these initial results are reassuring, as ICSI is used annually to overcome infertility in tens of thousands of cases worldwide.

Scientists Clarify Role of Calcium in Establishing Pregnancy -- A pregnancy becomes established only when the early embryo attaches itself to the uterus. Scientists have long known that a chemical "dialogue" between mother and embryo controls this critical event. Now researchers have decoded a key part of that conversation, and learned exactly how the embryo embeds itself inside the endometrium, the membrane lining the interior of the uterus. The early embryo, called a blastocyst, consists of a cell mass and a fluid-filled cavity that are surrounded by another layer of cells, the trophoblast. Researchers have discovered that, immediately before implantation occurs, endometrial cells produce a special protein called heparin-binding EGF-like growth factor (HB-EGF). This protein accelerates blastocyst development and initiates a chemical chain reaction that culminates in the trophoblast attaching to the uterus. Special receptors on the exterior surface of trophoblast cells bind with maternally produced HB-EGF. This linkage "tells" the blastocyst to activate a chemical channel that draws calcium away from the uterine lining. The loss of calcium disrupts the junctions between endometrial cells, creating

a weak point that the blastocyst can invade. Deeper insights into the basic biochemical processes governing critical stages of embryonic development will eventually enable clinicians to diagnose the causes of female infertility more accurately and develop new ways to prevent certain types of infertility.

A Mystery Solved: Progesterone's Role in Maintaining a Pregnancy -- Scientists have known that both the increased production of the hormone progesterone and the partial suppression of the maternal immune system are essential for maintaining a pregnancy. Yet these two mysterious biological events remained unlinked until recent research revealed that progesterone itself suppresses the manufacture of T-lymphocytes in the thymus gland. T-lymphocytes are immune-system cells that can attack "foreign" embryological tissue, threatening the survival of the fetus, if they continued to be produced in normal numbers. Scientists have discovered that the cells making up the deep interior tissues of the thymus gland possess receptors, or specialized surface molecules, that bind with progesterone. Once bound with progesterone, these interior cells disrupt the early stages of T-lymphocyte development in cells located on the surface of the thymus. While many other mechanisms are probably involved in suppressing the mother's immune system during pregnancy, it is now clear that progesterone's actions on thymus cells play a central role in this process. Uncovering the basic biological pathways involved in regulating the immune system and maintaining a pregnancy may allow scientists to clarify additional factors contributing to female infertility and to devise new therapies to prevent miscarriages.

Infectious Diseases: Protecting the Most Vulnerable Children

The worldwide burden of mortality and morbidity caused by infectious diseases is enormous, and is especially devastating in developing countries. The NICHD has long led the search for vaccines against infectious agents disproportionately affecting the health of infants, children and other vulnerable populations. Vaccines against pertussis and *Haemophilus influenzae* type B are among the Institute's most significant successes. To continue protecting vulnerable children throughout the world, the NICHD sponsors research on the biological processes at work in the developing immune system to clarify genetic and environmental factors that compromise its healthy development and function. In addition, NICHD researchers are studying the mechanisms through which microorganisms cause disease in an effort to find new preventive strategies and cost-effective therapies.

Scientists Find Immune Mechanism That Suppresses Leukemia -- Throughout life, white blood cells, a critical component of the immune system, begin developing from immature precursor cells in the bone marrow and complete their development in the thymus gland. Many genes and gene products, only a fraction of which are known, control this highly complex process. Scientists have recently studied the biological effects of one such gene product, interferon consensus binding protein (ICSBP), on the cellular immune system. They discovered that ICSBP is essential to the development of macrophages, a type of white blood cell that devours foreign organisms and constitutes one of the body's most powerful weapons against disease-causing microbes. By creating transgenic mice lacking ICSBP, the researchers also learned that this regulatory protein prevents the uncontrolled cell growth of another type of white blood cell that typically causes a condition similar to chronic myelogenous leukemia in humans. These insights into the function of ICSBP shed light on normal and abnormal immune-system development, on

the biochemical mechanisms involved in fighting infections, and on pathological processes leading to leukemia.

Zinc: A Low Cost Solution to Improving Children's Immune System -- In developing countries, seven out of ten childhood deaths can be attributed to pneumonia, diarrhea, measles, malaria, and malnutrition.[9] The prevalence of these illnesses is often due to impaired immune system function resulting from environmental factors common to the developing world, including chronic malnutrition. Zinc deficiency, in particular, is common among children in these countries. This nutrient normalizes cell functions in many different tissues and increases the number of white blood cells available to fight infection. NICHD-supported researchers assessed the results of recent controlled trials documenting the effects of zinc supplementation on malnourished infants and young children in seven developing countries. The researchers found that the incidence of diarrhea and dysentery can be decreased by as much as 27 percent; and that of pneumonia, by 41 percent. These findings strongly confirm the incalculable value of low-cost preventive strategy such as zinc supplementation in improving immune system function and increasing child survival rates in developing countries.

Promising Target for New Drugs Against Malaria -- Between 300 and 500 million people become ill with malaria each year, and the disease kills more than one million people annually.[10] Most victims live in developing countries, and the majority of these are under the age of five. Malaria-causing parasites are rapidly becoming increasingly resistant to standard drug therapies, posing an even greater threat to public health throughout the world. The parasite that causes the most serious form of human disease, *Plasmodium falciparum*, undergoes an essential stage of its complex life cycle inside human red blood cells. By developing an innovative method to examine how this organism affects the physical structure of red blood cells, scientists have learned that the parasite creates microscopic channels in these cells' outer membranes to access the nutrients it needs to survive. This discovery opens the way for developing new therapies targeting these nutrient channels and helps solve the problem of *P. falciparum*'s increasing resistance to current anti-malarial drugs. Moreover, further research based on this discovery is likely to lead to new vaccines that can prevent *P. falciparum* infection.

Basic Developmental Research: Shedding Light on Chronic and Degenerative Diseases
Scientists now know that many disorders (birth defects, cancers, or metabolic disorders) result when genetic or environmental factors alter basic developmental pathways. Research into how the human body normally develops and changes over time, a central component of the NICHD's mission, continues to increase scientists' understanding of the early origins of many diseases, leading to new methods of prevention and treatment. The Institute's ongoing commitment to this avenue of inquiry will continue to reduce the burden of chronic, often disabling illness that prevents many from leading fully productive lives.

Investigators Show Excess Iron May Contribute to Degenerative Neurological Disorders -- As a transporter of oxygen to cells throughout the body, iron is essential to life, and many biological

[9] World Health Organization: http://www.who.int/inf-fs/en/fact178.html

[10] World Health Organization Malaria Fact Sheet. http://www.who.int/inf-fs/en/fact094.html World Health Organization Malaria Fact Sheet. http://www.who.int/inf-fs/en/fact094.html

mechanisms regulate the amount present in body tissues. Too little iron results in oxygen starvation, but too much iron is equally toxic to cells and can lead to diseases such as atherosclerosis and chronic hepatitis. Scientists have long known that in many degenerative neurological disorders, possibly including Alzheimer's and Parkinson's diseases, excess iron accumulates in nerve cells, leading to further central nervous system damage. They do not know, however, whether excess iron causes or results from these disease processes. To answer this fundamental question, NICHD researchers recently studied mice genetically engineered to lack a key protein involved in iron metabolism. Scientists found that the mice, due to excess iron accumulation in brain tissues, developed a disease similar to a chronic human neurological disorder called Multiple System Atrophy. These results suggest that, at least in some degenerative nervous system disorders, excess iron accumulation can contribute to the disease process. Drugs already exist that can remove iron from the heart and the liver. Now, efforts are underway to design similar drugs that can cross the blood-brain barrier to prevent neuronal damage.

Primary Lymphoedema: Scientists Clarify Genetic Basis of A Chronic Disorder -- Primary lymphoedema, a progressive congenital disorder, causes persistent swelling in the extremities due to impaired circulation of lymphatic fluid. The lymphatic system is composed of vessels that circulate lymph--a pale fluid composed of plasma and white blood cells--throughout the body's tissues. In primary lymphoedema, lymphatic vessels are absent or abnormally narrow, blocking normal lymph flow. The chronic pooling of lymph in the arms or legs eventually leads to muscle deterioration, pathological skin changes, frequent infections, physical disability, and in the worst cases, cancer of lymphatic vessels. An acquired form ("secondary lymphoedema") sometimes results from flawed healing responses to traumatic or surgical injuries. Scientists believe that lymphatic development and function is regulated by a variety of unidentified genes, which, when mutated, may result in lymphoedema. Recently, researchers linked primary inherited lymphoedema to the gene for VEGFR-3, a growth factor that is important for activating normal lymphatic vessel formation and function. Now, scientists have also found mutations in this gene that are responsible for making the enzyme, tyrosine kinase, which plays a key role in signaling the growth of new lymphatic vessels. These results indicate that, in some cases, lymphoedema results from a mutation interfering with this critical signaling pathway. These findings not only shed light on the developmental biology of the lymphatic system, but also suggest new therapeutic approaches to lymphoedema, a condition that has always been difficult to treat. Knowing more about the genetic basis of this disorder may also reveal why some individuals develop the acquired form after injuries and lead to interventions to prevent its development.

Rare Genetic Disorder Sheds Light on Critical Pathway of Tumor Formation -- Investigations of rare genetic diseases such as Carney Complex (CNC), which causes tumor formation in multiple organ systems and disorders in skin pigmentation, often yield critical information about genetic factors regulating basic cell functions. In earlier studies, scientists identified two chromosomal locations that may harbor genes involved in CNC. The first site carries genes associated with tumor development. The second site carries genes involved in regulating protein kinase A, an enzyme that appears to be a tumor suppressor. Now investigators have discovered that a particular gene in the second chromosomal region is mutated in about 50 percent of all patients with CNC. This gene directs the synthesis of a regulatory subunit of protein kinase A. The discovery of this genetic mutation may lead to the development of new diagnostic aids to screen

individuals at risk of developing sporadic tumors and to new drugs to treat patients with CNC and other genetic or non-genetic tumors.

NEW RESEARCH OPPORTUNITIES

The NICHD's strategic plan, *From Cells to Selves,* spells out an ambitious but achievable course of research that reaffirms the Institute's leadership position in, and commitment to, the developmental and reproductive sciences. Based on the broad objectives outlined in this overview, the NICHD recently convened expert panels to advise us on future research opportunities. These ideas, which are set forth in four detailed "research agendas," will guide program administrators in developing future scientific initiatives to address biobehavioral development, developmental biology, reproductive health, and the fetal antecedents of disease susceptibility. In addition, the Institute recently published a strategic plan, *Health Disparities: Bridging the Gap*, which specifically targets research in areas that disproportionately affect minorities. Many of these promising initiatives, as highlighted in the selections below, will significantly advance scientific knowledge, improve public health and help to achieve equitable health outcomes for all populations.

HEALTH DISPARITIES: A Focus on Infant Mortality

Reducing Preterm Births Caused by Infection

A major priority for future research is to clarify the mechanisms that lead to racial and ethnic disparities in preterm birth, particularly among African-American women, who have the highest rate of preterm delivery. Preterm birth has been linked to a variety of factors, including genetics, stress, and intrauterine infection and inflammation. Recent studies suggest that intrauterine inflammation and infection may occur either before or quite early in pregnancy, although symptoms may not become evident until the second trimester of pregnancy. To better understand how infections lead to preterm birth and adverse neonatal outcomes, the NICHD will support basic studies in its intramural Perinatology Research Branch and clinical trials in its extramural research networks. Researchers will focus on infectious or inflammatory conditions that occur more frequently in certain ethnic groups, such as bacterial vaginosis, urinary tract infections, chronic endometritis and untreated periodontal disease. Researchers will also be encouraged to develop strategies that emphasize counseling women on how to prevent these infections *before* they become pregnant. Among newborns, research will be conducted on the clinical consequences of intrauterine infections, such as neonatal mortality and conditions affecting the newborn's respiratory system, brain, and digestive tract. To increase the participation of racial and ethnic populations in these studies, researchers will be encouraged to work with community hospitals that traditionally serve minority populations.

Reducing Sudden Infant Death Syndrome (SIDS) in Native American Communities

One of the Institute's top priorities is to continue to reduce the rate of infant mortality in the U.S., particularly deaths attributed to SIDS. While biomedical and public outreach initiatives have substantially reduced the incidence of SIDS over the past several years, disparities in SIDS deaths persist among certain minority populations. As efforts to intensify outreach to African-American communities continue, the Institute will expand its research efforts to Native American communities, where the highest SIDS rates in the U.S. are among American Indian (AI) tribes and Alaskan Native (AN) communities in the North Central and Northwestern states. New

evidence from the Aberdeen Area Infant Mortality Study, a case-control study of infant death, demonstrates a strong association of prenatal alcohol exposure with SIDS. Furthermore, some studies estimate that the prevalence of fetal alcohol syndrome among particular AI tribes and AN communities exceeds 25 percent. On some reservations, the prevalence of heavy drinking during pregnancy is over 70 percent. To further examine the association between alcohol consumption during pregnancy and SIDS, the NICHD will collaborate with the NIAAA and the at-risk AI/AN communities to examine how prenatal alcohol exposure affects the developing fetus. The long-term goal is to develop preventive and therapeutic strategies to protect the mother and her developing child.

REPRODUCTIVE HEALTH: New Research Directions for Women and Men

Uterine Fibroids

A key objective of the NICHD's strategic plan is identify new treatments for common reproductive problems in women such as endometriosis, polycystic ovary syndrome, and uterine fibroids. These conditions are often overlooked, yet they cause considerable morbidity, lowered fertility, and substantial economic burden. As a first step, the NICHD will expand its efforts to better define the causes and most appropriate treatment for uterine fibroids, the most frequently diagnosed tumor of the female pelvis. Uterine fibroids, although rarely cancerous, are a significant public health concern. Many women with fibroids experience symptoms ranging from abnormal uterine bleeding and pelvic pain to anemia and infertility. While new medical and surgical interventions are emerging, uterine fibroids remain the number one reason for hysterectomy. Researchers conservatively estimate that 15 million, or 25 percent[11] of U.S. women of reproductive age, have clinical symptoms from these tumors. According to some estimates, fibroids are diagnosed in African-American women two to three times more frequently than in White women. However, the factors that initiate uterine fibroid growth are not known. Since better understanding of this process will help preserve the fertility and reproductive health of millions of women, the Institute will support studies to determine what causes uterine fibroids to grow. The NICHD will also support clinical trials to evaluate pharmaceutical treatments, to assess the complication rates and benefits of different surgical approaches, and to understand how uterine fibroids affect a woman's quality of life. Throughout the initiative, investigators will be expected to collaborate with community-based practitioners to assure diversity among the research team and help recruit minority women.

Male Reproductive Health and Contraceptive Development

As exciting new advances begin to rapidly change the face of male contraception and infertility research, the NICHD plans to devote new resources to this important area. The goal is to provide men with new contraceptive options as well as reliable, cost-effective ways to prevent, diagnose, and treat male reproductive conditions. The Institute will support collaborative biomedical and behavioral research projects to design innovative approaches to male contraception, and to evaluate the acceptability of existing and potential new male contraceptive products. As products are developed, the NICHD will provide the resources needed to evaluate their safety and efficacy, a step which is crucial to securing FDA approval for marketing. Finally, the Institute

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[11]Newbold RR, DiAugustine RP, Risinger JI, Everitt JI,Walmer DK, Parrott EC, Dixon D: Advances in uterine leiomyoma research: conference overview, summary, and future research recommendations. Environ Health Perspect. 108 Suppl 5:769-73, 2000.

will support career-training grants to develop a new cadre of clinician investigators who are dedicated to advancing male reproductive and contraceptive health research.

Behavioral Interventions for Preventing Pregnancy and Sexual Transmitted Disease (STDs). A critical element of the NICHD's strategic plan on reproductive health involves improving contraceptive use and services. One out of every two pregnancies to U.S. women is unintended and one in five ends in abortion. Previous NICHD-supported research on this topic has documented a wide range of factors that contribute to unintended pregnancy, including concerns about health effects of contraceptive methods, relationships with partners and partners' attitudes, and cultural, institutional, and economic barriers in accessing services. While these studies provide useful insights for designing some kinds of prevention efforts, researchers need more detailed information to address *specific* barriers to contraceptive use and to inform practitioners regarding the most effective way to deliver services. Thus, the NICHD will support basic research on the specific factors that influence the decision to continue, discontinue, or switch contraceptive methods. Researchers will also evaluate how the attitudes and beliefs of healthcare providers shape their interactions with patients, and ultimately, the patient's decisions about contraceptive use. Other studies will focus on issues such as how the organization and delivery of family planning services may influence an individual's decision to seek services. Based on this information, researchers will be encouraged to develop interventions that are culturally sensitive, cost-effective, and sustainable within the particular setting or community that is being targeted.

Related research will focus specifically on reducing sociocultural barriers to preventing STD's and other reproductive tract infections, which disproportionately affect minority communities. While all of these diseases can be prevented, treated, and in some cases cured, the sociocultural barriers that prevent individuals from seeking treatment are harder to change. For instance, gender, race, ethnicity, and cultural values may all influence decisions to make use of available health care. The NICHD will support novel, investigator-initiated research on behaviors related to preventing and treating STDs, emphasizing sociocultural perspectives and beliefs both among women at risk of STDs and their partners. Future studies will also examine the behavior of healthcare providers to identify other barriers to preventing STDs, such as differences in the way healthcare providers in clinics and private-based practices screen for and report STDs, or potential biases they may hold about treating certain populations.

DEVELOPMENTAL BIOLOGY: Understanding Our Fundamental Selves

Animal Models of Birth Defects

To bring us closer to realizing an important goal of the Institute's Birth Defects Initiative, the NICHD will support new and expanded animal studies to better understand the underlying mechanisms of early development. This will include studies to evaluate a new model of embryonic development, called *X. tropicalis*. *X. tropicalis* is a species of *Xenopus,* or frog, which has long served as a model of embryonic development because it develops externally, is easy to visualize, and is able to withstand scientific experimentation. Preliminary data indicate that *X. tropicalis* offers a more promising opportunity to understand how birth defects occur. This is because it has a chromosomal structure that is closer to that of humans and reproduces in a shorter period of time. However, before the scientific community will widely adopt this model, researchers need to determine whether its genes can be easily mutated and if the resulting

mutations will be passed on and maintained through several life cycles. If these studies are successful, the NICHD will be able to provide researchers with a more efficient means for conducting developmental research.

Similarly, the Institute will support additional facilities specifically designed to produce large numbers of mice with developmental defects. Because mice and humans share many of the same developmental genes and processes, researchers have been creating mutant mice with the same malformations as known human birth defects. However, the number of facilities conducting these studies is limited. This expansion will allow researchers to produce and distribute large numbers of mutant mice, enabling researchers to quickly and efficiently define the genetic causes of birth defects.

BIOBEHAVIORAL RESEARCH: Linking Biology to Behavior

Biobehavioral Studies of Developmental Disabilities

One of the most challenging problems in managing and treating developmental disabilities is self-injurious behavior (SIB). Up to 20 percent of all people with intellectual and other developmental disabilities engage in repetitive SIB, and 40-50 percent of individuals with autism injure themselves.[12] Children with SIB may also direct aggressive behavior at others. Although scientists have learned much about the *individual* genetic, neurobiological, and environmental factors related to SIB, more needs to be learned about how these specific factors *interact* to trigger SIB. Based on recommendations from a recent NICHD-sponsored workshop on this topic, the Institute will support studies to unravel the complex interactions that lead to SIB, including how alterations in neurological "circuitry" in multiple brain regions may cause SIB.

Adolescence: Understanding the Complex Interactions That Shape Behavior

Biobehavioral studies of adolescence are also a high priority for future research. Other than the first three years of life, there is probably no other time when developmental changes occur so rapidly and so profoundly as during the teen years. Adolescence is often marked by stark contrasts in behavior, ranging from emotional mood swings and poor judgement to tremendous accomplishment in social and learning behavior. Clinicians generally agree that the physiological and psychological changes during adolescence can significantly influence how teens think, interact with others, and regulate their own behavior. Unfortunately, there is little scientific knowledge concerning the underlying processes that drive development during these years. To better understand these processes, the NICHD will support research to understand how interactions between the brain, hormones, and environmental stimuli lead to changes in teen behavior at the onset of adolescence and into young adulthood. Researchers will also examine how these processes interact with such external factors as peers, family, and the community to expand our scientific understanding of this complex developmental period.

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[12]Schroeder SR, Oster-Granite ML, Berkson G, Bodfish JW, Breese GR, Cataldo MF, Cook EH, Crnic LS, Fisher W, Harris JC, Horner RH, Iwata B, Jinnah HA, King BH, Lauder JM, Lewis MH, Newell K, Nyhan WL, Rojahn J, Sackett GP, Sandman C, Symons F, Tessel RE, Thompson T, and Wong DF: Self-Injurious Behavior: Gene-Brain-Behavior Relationships. Mental Retardation and Developmental Disabilities Research Reviews, 2001. In press.

GENETIC BASIS OF DISEASE SUSCEPTIBILITY: Stopping Disease Before It Begins

Gene Expression Throughout Development

To understand how genes and environmental factors interact to produce childhood and adult-onset disease, the NICHD is initiating several new projects. The first project will help us better understand the underlying mechanisms of development by clarifying how genes are activated, or "expressed" as an individual develops, grows, and matures. While advances from the Human Genome Project have provided an important first step by mapping out the location of thousands of genes, scientists still do not know the function of many genes and why their expression varies in different people, in different environments, and across different periods of development. Using novel scientific methods, researchers will be able to determine how genes are activated to perform specific functions by internal and external "signals" throughout the course of development. Once this data is obtained, they will then be able to compare how genes are expressed in "normal" circumstances to how genes are expressed when an error occurs. Ultimately, this data will provide vital information for determining what specifically goes wrong in a variety of diseases and disorders.

Identifying Genetic Factors Leading to Preterm Birth

Another initiative will make use of research resources, such as DNA chip technology and animal models, to specifically examine genetic factors that may contribute to preterm delivery. Future research on this topic will include identifying genetic markers in families with a history of multiple preterm births and identifying variations of genes that may be associated with susceptibility to premature labor. Other studies will focus on identifying genes that may stimulate an immune response to uterine infection and inflammation, and ultimately lead to premature labor. Researchers will also try to identify novel genes that may regulate fetal growth. Collectively, these studies will contribute to the Institute's efforts to reduce infant mortality, reduce health disparities, and further delineate the genetics of disease susceptibility.

HIV/AIDS

Adolescents and AIDS

To continue its past scientific achievements in HIV/AIDS research, the NICHD will expand studies that enhance the lives of women, children, and families who are at risk of HIV/AIDS. Starting with teens, the NICHD will expand previous activities by supporting a unique Adolescent Medicine Trials Network for HIV/AIDS. This collaborative effort involves prevention studies and appropriate anti-retroviral therapy trials targeting high-risk adolescents. Additional interventions targeting HIV prevention among preteens also will be funded.

Women and AIDS

To better understand the impact of HIV infection in women, the NICHD also will continue its support of the Women's Interagency HIV Study. Other NICHD efforts targeting the needs of high risk women include 1) the multinational study, *Hormonal Contraception and Risk of AIDS/HIV Transmission*, which examines the effects of hormonal contraceptives on the susceptibility of uninfected women to HIV transmission and progression; and 2) the HIV Pathogenesis Program, which will examine the causal relationships between HIV pathogenesis and factors unique to women, with a focus on minority women. Complementing these projects, the Institute will implement its updated strategic plan on contraceptive microbicides. Collaborative efforts will include the development of an array of novel, non-vaccine,

microbicidal products, with or without contraceptive activity, to prevent the sexual transmission of HIV, and new models to assess their effectiveness. Finally, new projects should help coordinate and track microbicidal products as they are developed, and standardize and validate pre-clinical tests.

International AIDS

As part of its global commitment to HIV/AIDS research, particularly in developing countries where the need is most urgent, the NICHD plans to establish a new program, *Global Partnerships for AIDS Research in Women, Children, and Families.* This program will expand international research that complements intervention studies such as those concerning the safety and tolerability of anti-retroviral prophylaxis; clinical trials on the effect of breast-feeding on HIV transmission; and the effect of vitamins and micronutrients on reducing the rate of HIV transmission and the severity of disease progression. Related efforts include support for the collaborative HIV Prevention Trials Network, as well as a new project examining nutrition, care, and management of HIV-affected women and children in sub-Saharan Africa.

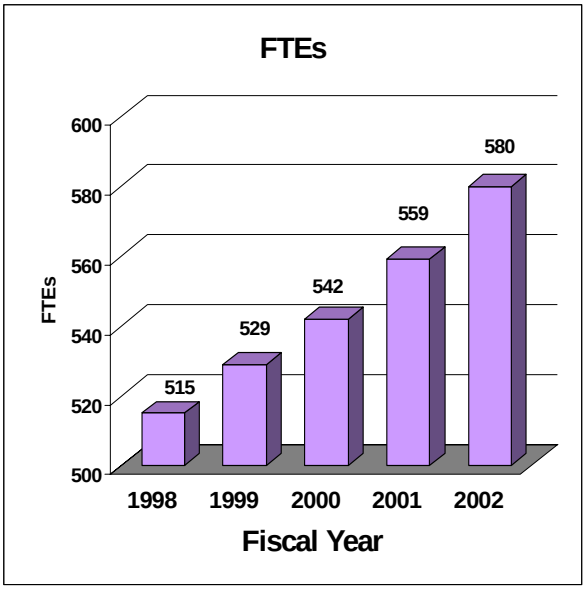
Behavioral/ Social Sciences, and Training

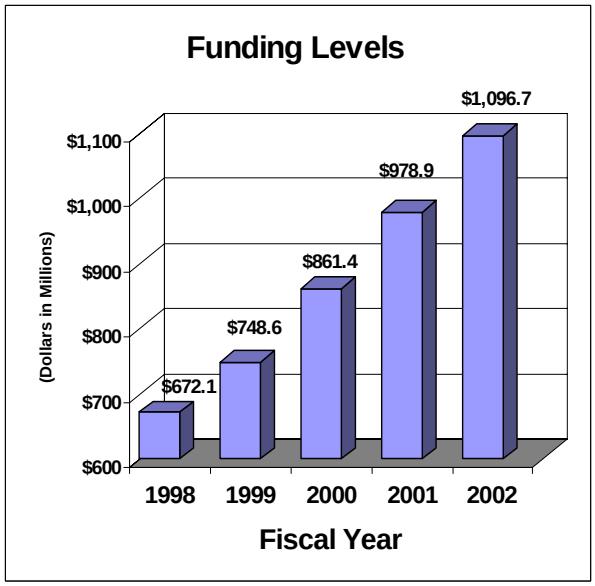
The NICHD recognizes that behavioral and social science research, as well as the training of new investigators, are key to meeting the future challenges posed by the HIV epidemic. To address these needs, the Institute plans to integrate HIV/AIDS training and career development into its behavioral and social science projects. Collaborative efforts between minority and non-minority institutions will be encouraged. The NICHD will also work with the Fogarty International Center to include behavioral and social science research in its HIV-related, international training programs. In addition, new research will focus on the role of community-based institutions -- such as churches, schools, social service agencies, and local government organizations -- in developing innovative, science-based, HIV prevention efforts. Another initiative will invite researchers to examine how individuals and their sexual partners, from different international settings and cultural backgrounds, interpret prevention messages and put them into practice.

BUDGET POLICY

The FY 2002 budget request for the NICHD is $1,096,650,000, including AIDS, an increase of $117,744,000 and 12 percent over the FY 2001 level, and $235,290,000 and 27.3 percent over FY 2000.

A 5 year history of FTEs and funding levels for NICHD are displayed in the graphs on the following page.





One of NICHD's highest priorities is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while providing new research opportunities. The FY 2002 request provides average cost increases for competing RPGs equal to the Biomedical Research and Development Price Index (BRDPI), estimated at 4.3 percent. Noncompeting RPGs will receive increases of 3 percent on average for recurring direct costs. In FY 2002, total RPGs funded will be 1,825 awards, an increase of 114 awards over the FY 2001 estimate, the highest annual total ever awarded.

Promises for advancement in medical research are dependent on a continuing supply of new investigators with new ideas. In the FY 2002 request, NICHD will support 849 pre- and postdoctoral trainees in full-time training positions. An increase of 10 percent over FY 2001 levels is provided for stipends and training-related expenses (e.g., health insurance, research supplies and equipment, and travel to scientific meetings).

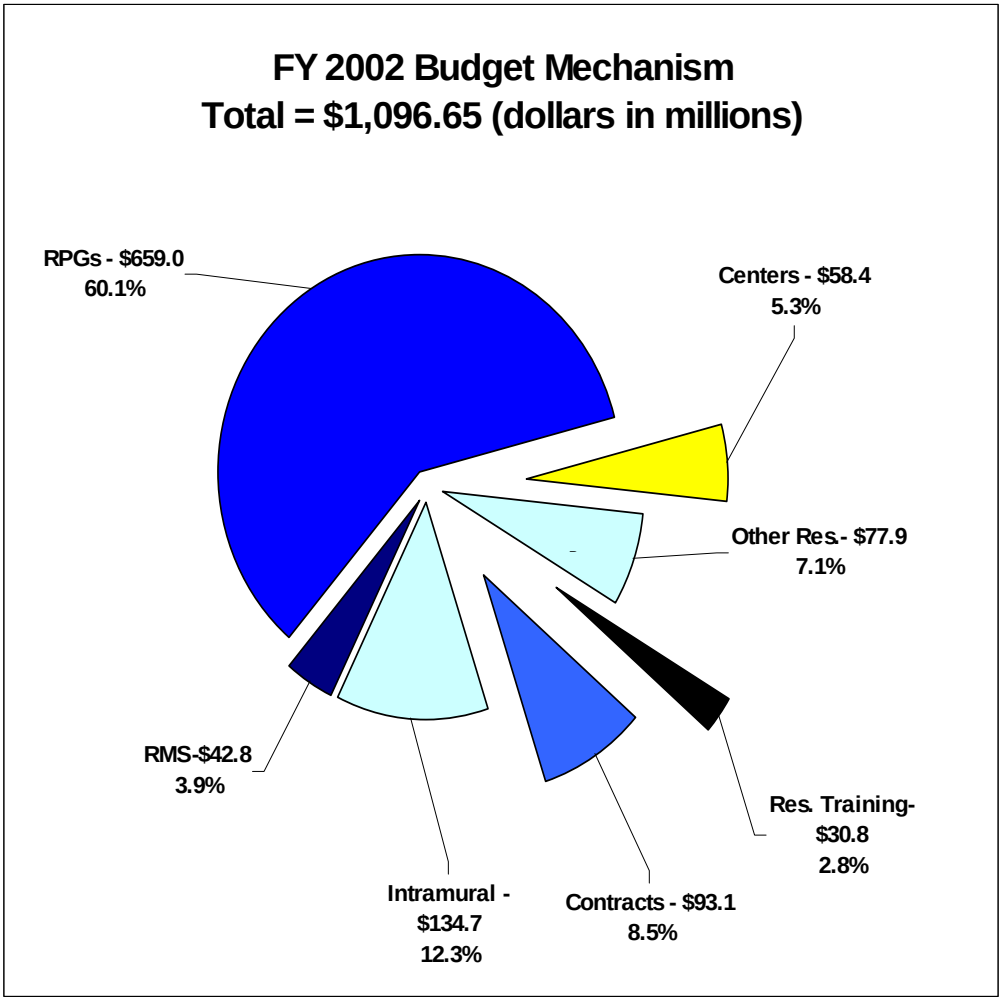
The Extramural Associates Research Development Award program (EARDA) is a competitive grant program that provides support for developing research infrastructure at domestic private and public women's colleges and at institutions of higher education that have significant numbers of under-represented minority students. This program, which began in FY 1994, was initially administered by the NIH Office of Extramural Programs. In June of FY 2000, administration of the program was reassigned to the NICHD while funding for this program remained with the NIH Office of the Director and was provided to the NICHD through an intra agency agreement. Beginning in FY 2002, the funds to support this program are included in the NICHD budget estimate rather than in the budget estimate for the NIH Office of the Director.

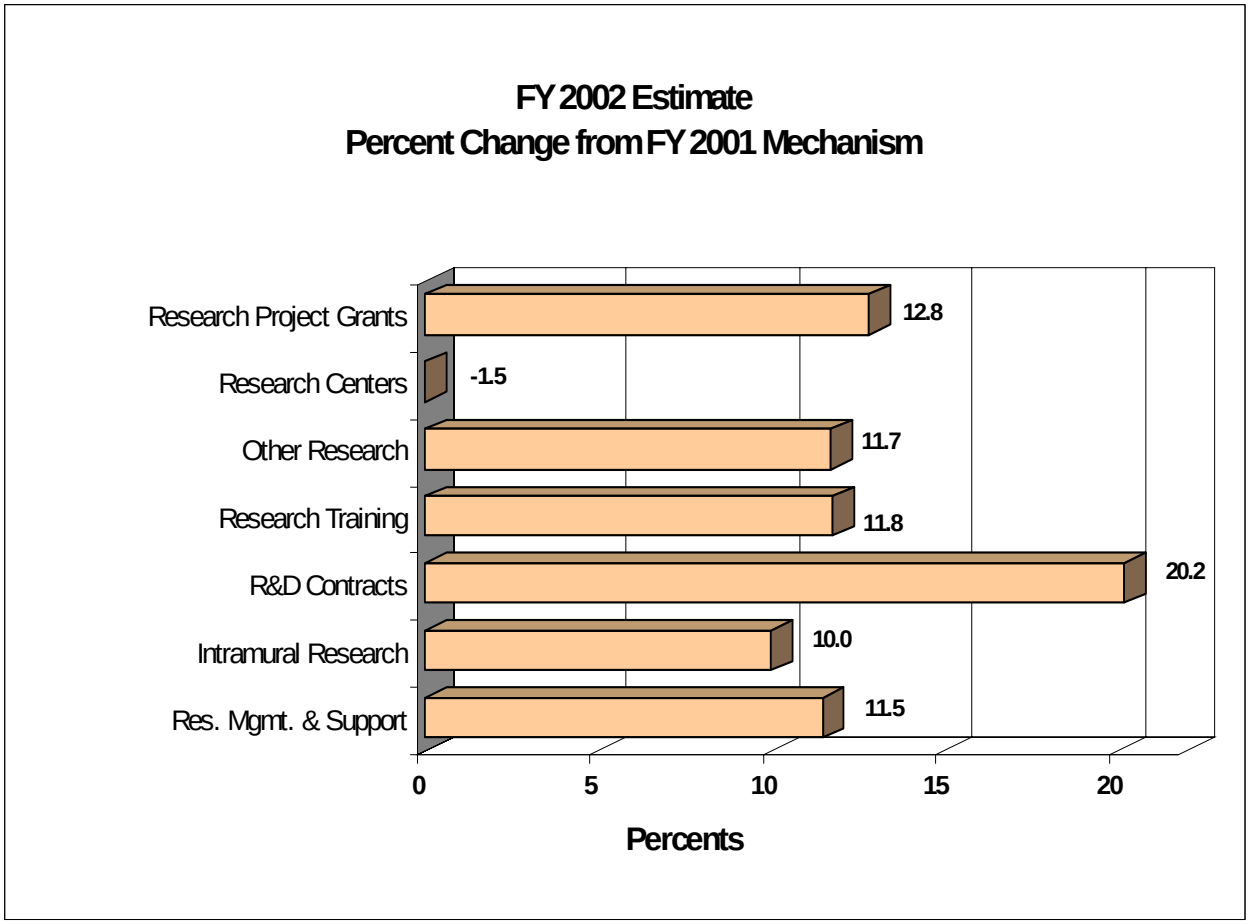
The FY 2002 request includes funding for 55 research centers, 435 other research grants, and 106 R&D contracts. Within the R&D contracts mechanism, $3,111,000 is included for the new Extramural Clinical and Pediatric Loan Repayment Programs and continuation of the NICHD loan repayment program for contraceptive and infertility research. In addition, the R&D contract

mechanism includes funding for a new contract in support of the NICHD Intramural Perinatology Branch.

Intramural Research and Research Management and Support will be supported with increases of 10 and 11.5 percent, respectively. A major thrust in expansions in the NICHDs program of intramural research deals with biological regulation and consequences of processes of growth and differentiation. Specific areas encompassed in these efforts are: DNA repair, developmental neurobiology, endocrine and reproductive biology. Concerted research efforts are directed at the heritable, genetic and epigenetic basis of these developmental phenomena. Increases in the Research Management and Support Funding Mechanism will ensure the effective management of the Institute's expanding extramural program and provide for critical improvements in information technology and other infrastructure requirements.

Funding mechanism distributions by dollars and percent change are displayed in the graphs below and on the following page.




FY 2002 Estimate
Percent Change from FY 2001 Mechanism
Research Project Grants
Research Centers
Other Research
Research Training
R&D Contracts
Intramural Research
Res. Mgmt. & Support
12.8
-1.5
11.7
11.8
20.2
10.0
11.5
0
5
10
15
20
Percents

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Budget Mechanism

MECHANISM	FY 2000 Actual		FY 2001 Estimate		FY 2002 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	1,073	$350,809,000	1,136	$405,019,000	1,245	$470,115,000
Administrative supplements	(73)	2,857,000	(75)	3,028,000	(75)	3,133,000
Competing:						
Renewal	117	50,762,000	123	55,552,000	125	60,184,000
New	325	85,116,000	348	98,106,000	348	100,604,000
Supplements	7	1,099,000	7	1,077,000	7	1,160,000
Subtotal, competing	449	136,977,000	478	154,735,000	480	161,948,000
Subtotal, RPGs	1,522	490,643,000	1614	562,782,000	1725	635,196,000
SBIR/STTR	94	18,810,000	97	21,300,000	100	23,800,000
Subtotal, RPGs	1,616	509,453,000	1711	584,082,000	1825	658,996,000
Research Centers:						
Specialized/comprehensive	70	57,983,000	64	59,230,000	55	58,315,000
Clinical research	0	0	0	0	0	0
Biotechnology	0	100,000	0	100,000	0	100,000
Comparative medicine	0	0	0	0	0	0
Research Centers in Minority Institutions	0	0	0	0	0	0
Subtotal, Centers	70	58,083,000	64	59,330,000	55	58,415,000
Other Research:						
Research careers	169	15,700,000	260	24,500,000	290	28,380,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	52	25,309,000	62	32,414,000	62	33,700,000
Biomedical research support	0	0	0	0	0	0
Minority biomedical research support	0	855,000	0	971,000	0	1,080,000
Other	74	10,348,000	78	11,785,000	83	14,691,000
Subtotal, Other Research	295	52,212,000	400	69,670,000	435	77,851,000
Total Research Grants	1,981	619,748,000	2175	713,082,000	2315	795,262,000
Training:	FTTPs		FTTPs		FTTPs	
Individual awards	130	4,909,000	135	5,410,000	137	5,942,000
Institutional awards	674	20,495,000	684	22,156,000	712	24,872,000
Total, Training	804	25,404,000	819	27,566,000	849	30,814,000
Research & development contracts	76	72,645,000	80	77,482,000	106	93,145,000
(SBIR/STTR)	(0)	(0)	(0)	(0)	(0)	(0)
	FTEs		FTEs		FTEs	
Intramural research	333	109,295,000	350	122,410,000	365	134,651,000
Research management and support	209	34,268,000	209	38,366,000	215	42,778,000
Cancer prevention & control	0	0	0	0	0	0
Construction		0		0		0
Total, NICHD	542	861,360,000	559	978,906,000	580	1,096,650,000
(Clinical Trials)		116,042,000		132,000,000		147,800,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Budget Authority by Activity
(dollars in thousands)

ACTIVITY	FY 2000 Actual		FY 2001 Estimate		FY 2002 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural research		$717,797		$818,130		$919,221		$101,091
Intramural research	333	109,295	350	122,410	365	134,651	15	12,241
Research management and support	209	34,268	209	38,366	215	42,778	6	4,412
Total	542	861,360	559	978,906	580	1,096,650	21	117,744

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Summary of Changes

2001 Estimated budget authority				$978,906,000
2002 Estimated budget authority				1,096,650,000
Net change				117,744,000
	2001 Current Estimate Base		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$43,079,000		$580,000
b. Annualization of January 2001 pay increase		43,079,000		398,000
c. January 2002 pay increase		43,079,000		1,179,000
d. One day more pay		43,079,000		174,000
e. Payment for centrally furnished services		22,761,000		2,276,000
f. Increased cost of laboratory supplies, materials, and other expenses		56,570,000		2,372,000
Subtotal				6,979,000
2. Research Management and Support:				
a. Within grade increase		18,921,000		283,000
b. Annualization of January 2001 pay increase		18,921,000		175,000
c. January 2002 pay increase		18,921,000		518,000
d. One day more pay		18,921,000		77,000
e. Payment for centrally furnished services		4,097,000		410,000
f. Increased cost of laboratory supplies, materials, and other expenses		15,348,000		727,000
Subtotal				2,190,000
Subtotal, Built-in				9,169,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Summary of Changes--continued

CHANGES	2001 Current Estimate Base No.	2001 Current Estimate Base Amount	Change from Base No.	Change from Base Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	1136	408,047,000	109	65,201,000
b. Competing	478	154,735,000	2	7,213,000
c. SBIR/STTR	97	21,300,000	3	2,500,000
Total	1711	584,082,000	114	74,914,000
2. Centers	64	59,330,000	(9)	(915,000)
3. Other research	400	69,670,000	35	8,181,000
4. Research training	819	27,566,000	30	3,248,000
5. Research and development contracts	80	77,482,000	26	15,663,000
Subtotal, extramural				101,091,000
	FTEs		FTEs	
6. Intramural research:	350	122,410,000	15	5,262,000
7. Research management and support	209	38,366,000	6	2,222,000
Subtotal, program		978,906,000		108,575,000
Total changes	559		21	117,744,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development
Budget Authority by Object

	FY 2001 Estimate	FY 2002 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	559	580	21
Full-time equivalent of overtime and holiday hours	3	3	0
Average ES salary	$133,100	$138,400	$5,300
Average GM/GS grade	11.1	11.1	0.0
Average GM/GS salary	$64,500	$67,500	$3,000
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	$61,900	$64,300	$2,400
Average salary of ungraded positions	$88,000	$91,500	$3,500

	OBJECT CLASSES	FY 2001 Estimate	FY 2002 Estimate	Increase or Decrease
	Personnel Compensation:			
11.1	Full-Time Permanent	$27,519,000	$30,308,000	$2,789,000
11.3	Other than Full-Time Permanent	11,280,000	12,423,000	1,143,000
11.5	Other Personnel Compensation	1,750,000	1,927,000	177,000
11.8	Special Personnel Services Payments	10,481,000	12,000,000	1,519,000
11.9	**Total Personnel Compensation**	**51,030,000**	**56,658,000**	**5,628,000**
12.0	Personnel Benefits	10,966,000	12,077,000	1,111,000
13.0	Benefits for Former Personnel	4,000	4,000	0
	Subtotal, Pay Costs	**62,000,000**	**68,739,000**	**6,739,000**
21.0	Travel & Transportation of Persons	2,050,000	2,160,000	110,000
22.0	Transportation of Things	280,000	300,000	20,000
23.1	Rental Payments to GSA	0	0	0
23.2	Rental Payments to Others	584,000	610,000	26,000
23.3	Communications, Utilities & Miscellaneous Charges	2,050,000	2,250,000	200,000
24.0	Printing & Reproduction	1,320,000	1,450,000	130,000
25.1	Consulting Services	2,000,000	2,120,000	120,000
25.2	Other Services	10,200,000	11,200,000	1,000,000
25.3	Purchase of Goods & Services from Government Accounts	79,940,000	97,040,000	17,100,000
25.4	Operation & Maintenance of Facilities	1,800,000	1,950,000	150,000
25.5	Research & Development Contracts	62,880,000	75,455,000	12,575,000
25.6	Medical Care	2,000,000	2,050,000	50,000
25.7	Operation & Maintenance of Equipment	1,100,000	1,150,000	50,000
25.8	Subsistence & Support of Persons	0	0	0
25.0	**Subtotal, Other Contractual Services**	**159,920,000**	**190,965,000**	**31,045,000**
26.0	Supplies & Materials	12,219,000	13,500,000	1,281,000
31.0	Equipment	8,000,000	9,100,000	1,100,000
32.0	Land and Structures	0	0	0
33.0	Investments & Loans	0	0	0
41.0	Grants, Subsidies & Contributions	730,483,000	807,576,000	77,093,000
42.0	Insurance Claims & Indemnities	0	0	0
43.0	Interest & Dividends	0	0	0
44.0	Refunds	0	0	0
	Subtotal, Non-Pay Costs	**916,906,000**	**1,027,911,000**	**111,005,000**
	Total Budget Authority by Object	**978,906,000**	**1,096,650,000**	**117,744,000**

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Salaries and Expenses

OBJECT CLASSES	FY 2001 Estimate	FY 2002 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	$27,519,000	$30,308,000	$2,789,000
Other Than Full-Time Permanent (11.3)	11,280,000	12,423,000	1,143,000
Other Personnel Compensation (11.5)	1,750,000	1,927,000	177,000
Special Personnel Services Payments (11.8)	10,481,000	12,000,000	1,519,000
Total Personnel Compensation (11.9)	**51,030,000**	**56,658,000**	**5,628,000**
Civilian Personnel Benefits (12.0)	10,966,000	12,077,000	1,111,000
Benefits to Former Personnel (13.0)	4,000	4,000	0
Subtotal, Pay Costs	**62,000,000**	**68,739,000**	**6,739,000**
Travel (21.0)	2,050,000	2,160,000	110,000
Transportation of Things (22.0)	280,000	300,000	20,000
Rental Payments to Others (23.2)	584,000	610,000	26,000
Communications, Utilities and Miscellaneous Charges (23.3)	2,050,000	2,250,000	200,000
Printing and Reproduction (24.0)	1,320,000	1,450,000	130,000
Other Contractual Services:			
Advisory and Assistance Services (25.1)	2,000,000	2,120,000	120,000
Other Services (25.2)	10,200,000	11,200,000	1,000,000
Purchases from Govt. Accounts (25.3)	54,938,000	61,345,000	6,407,000
Operation & Maintenance of Facilities (25.4)	1,800,000	1,950,000	150,000
Operation & Maintenance of Equipment (25.7)	1,100,000	1,150,000	50,000
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**70,038,000**	**77,765,000**	**7,727,000**
Supplies and Materials (26.0)	12,205,000	13,486,000	1,281,000
Subtotal, Non-Pay Costs	88,527,000	98,021,000	9,494,000
Total, Administrative Costs	**150,527,000**	**166,760,000**	**16,233,000**

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

SIGNIFICANT ITEMS IN HOUSE, SENATE AND CONFERENCE APPROPRIATIONS COMMITTEE REPORTS

FY 2001 House Appropriations Committee Report Language (H. Rpt. 106-645)

Item

Chromosome 18 - The Committee commends the Institute for its efforts over the past year to encourage new scientific work into molecular, genetic, clinical, and therapeutic aspects of chromosomal abnormalities. The Committee continues to urge NICHD to seek ways to expand and intensify such research, especially studies involving the syndromes of chromosome 18. (p. 75)

Action taken or to be taken

Genetic disorders rank among the leading causes of mental retardation and developmental disabilities. These disorders are addressed by NICHD through support of studies of the location, organization, and regulation of the genetic material, as well as aberrations associated with chromosome number, morphology, or structure.

NICHD staff continues its efforts to stimulate additional research in syndromes associated with Chromosome 18. The Institute is working with research groups in San Antonio to develop meritorious research proposals in both basic and clinical research areas, including therapeutic trials, involving the San Antonio patient population base identified by the Chromosome 18 Registry and Research Society.

To stimulate the submission of new research proposals associated with syndromes involving Chromosome 18, NICHD staff have been actively involved in an educational outreach with the patient advocacy groups through presentations at the annual meeting of the Chromosome 18 registry. Here NICHD staff made presentations explaining funding mechanisms available for researchers applying to the NIH as well as explaining the general processes associated with the grant review process. NICHD staff is planning to convene a meeting of select invited participants in the summer of 2001. This “state of the science” meeting will bring together basic and clinical investigators familiar with syndromes associated with Chromosome 18, as well as basic and clinical investigators with expertise from other areas of research with direct relevance to disorders of chromosome 18. This meeting will establish a consensus of the state of research in the study of disorders associated with chromosome 18. It will also identify critical areas of research where fundamental knowledge of these disorders is lacking.

In December 1999, the NICHD sponsored a "Workshop on Self -Injurious Behavior." The participants in this workshop discussed and evaluated current studies and therapeutic strategies to ameliorate or prevent this important clinical symptom associated with many chromosomal disorders, including autism, Rett Syndrome, Lesch-Nyhan Disease, and other compulsive disorders. A summary report of this conference, entitled "Self-Injurious Behavior: Gene-Brain-Behavior Relationships" has been prepared and is currently in press in *Mental Retardation and Developmental Disabilities Research Reviews.* A book containing chapters summarizing the presentations has also been prepared, *Self-Injurious Behavior: Gene-Brain-Behavior Relationships,* and will be published by APA Books. NICHD will delineate those new research areas which would benefit from focus of attention, and determine whether other model systems can address neurological/behavioral issues associated with self-injurious behavior among MRDD populations.

A Conference on "Kleinfelter's Syndrome: New Research Directions" was held in August 2000. The purpose of the conference was to summarize current knowledge concerning the incidence of Kleinfelter's syndrome and its genetic basis. Participants at this conference summarized the spectrum of clinical features, reviewed current treatment and management practices, and considered ethical and counseling issues, and summarized current beliefs concerning the biological basis of functional defects. Based on their recommendations, NICHD will identify those new research areas which would benefit from focus of attention, and determine whether animal models can address neurological/behavioral issues and help clarify the endocrine dysfunction associated with Kleinfelter's syndrome.

A "Consensus Development Conference on Phenylketonuria (PKU): Screening and Management" was held October 16-18, 2000. The panelists and participants discussed the incidence and prevalence of PKU and other known forms of hyperphenylalanemia and the genetic and clinical variability associated with PKU and hyperphenylalanemia. They discussed the available newborn screening strategies and their effectiveness and the cost effectiveness of the screening and treatment measures currently available. Focus was then directed to the treatment regimens used to prevent adverse consequences of PKU and their effectiveness with respect to such variables as time of initiation of dietary compliance, duration of dietary management, and dietary regimen for women of childbearing age and other adults. The panel recommended that metabolic control be maintained throughout life and that consistent policies be established among state programs that deal with these patients. At a press conference at the conclusion of the Conference, the Conference Chair indicated that although PKU has been treated for 40 years and screening methods are remarkably effective, there still remain many questions to be answered.

The near completion (99.7%) of the sequence of human Chromosome 21 was announced in May, 2000 with the revelation that the chromosome contains only about 240 genes, many fewer than expected. To finish the conversion of draft sequence into final sequence, the Consortium sequencing Chromosome 21 has agreed to direct efforts to completion of the sequence and its distribution to the scientific community by spring, 2001. This landmark accomplishment, supported by various funding mechanisms at NICHD and other NIH institutes will enable investigators not only to identify genes relevant to Down Syndrome, but to facilitate creation of

animal models to study the effects that altered expression of specific genes located on chromosome 21 have on growth and development of various organs, particularly the brain.

Several program projects associated with chromosomal disorders continue to make substantial progress in their respective areas. One group of investigators studying the genetic disorders associated with peroxisomal abnormalities, such as adrenoleukodystrophy, an X-chromosome linked disorder, have demonstrated "pharamacological gene therapy" by treating patients with 4-phenylbutyrate, which leads to a substantial reduction in very-long-chain fatty acid levels in the brain and adrenal glands of a mouse model of the condition. Another group of scientists who focus on amino acid disorders associated with mental retardation and developmental disabilities have succeeded in developing an animal model for glutaric acidemia type 1 (GA 1). Existing Center programs have also been approved to undertake cooperative research in "Clinical Developmental Pharmacology of MRDD, Including Self-Injurious Behavior" and projects associated with "Pediatric Functional Neuroimaging in Mental Retardation and Developmental Disabilities".

A Program Announcement (PA) entitled "Rett Syndrome: Genetics, Pathophysiology, and Biomarkers" was reissued in January 2000. Responses to that PA are currently under review. Molecular studies by NICHD-supported investigators that had previously mapped the gene responsible for Rett Syndrome to the distal end of the long arm of the X chromosome, resulted last year in the identification of one such gene, MeCP2. Because MeCP2 is a gene expressed early in development, and mice mutant for MeCP2 fail to complete development to be live born, studies directed towards the manipulation of the MeCP2 gene, that would enable one to slow, reverse, or even prevent, the progression of Rett Syndrome are of great interest.

Item

Demographic Research - The Committee commends NICHD for its support for research on the causes of demographic trends and their impact on our society. The availability of objective information about such topics as declining marriage rates, fatherhood, teen childbearing, health disparities, welfare to work transitions, and the causes and impact of migration within and across our borders remains a priority. The Institute is encouraged to enhance efforts in the training and development of new demographic scientists and assure continued support for research infrastructure...(p. 75/76)

Action taken or to be taken

NICHD-supported demographic research continues to produce a wealth of objective scientific information on important trends affecting our society , their causes, and their consequences for the well-being of individuals and families. In the past year, cutting-edge demographic research has documented the social and economic forces underlying marriage trends; mapped the consequences of increasing nonmarital cohabitation for family instability experienced by children; produced data never before available on the education, language skills, and health of legal immigrants to the United States; and examined the role of risk and protective factors in producing favorable infant health outcomes among Puerto Ricans who have recently migrated to the mainland U.S. Other research has produced, for the first time, evidence that interventions

that combine comprehensive sex education with community service can produce long-term delays in the initiation of sexual activity among young people.

NICHD's investment in research on fatherhood is producing new knowledge about fathers in disadvantaged families. Results from a study of births to unmarried couples in urban areas across the U.S. also show high levels of father involvement early in the child's life. Nearly half of all such mothers were cohabiting with the father of their baby, and 36% were romantically involved but living apart. Most fathers contributed financially during the pregnancy, planned to stay involved with the mother and their child, and three-fourths reported a "pretty good" or "almost certain" chance of marrying the mother. Continued observation of these families over the next few years will identify those factors that enable fathers to remain committed to and involved with their new families. In addition, NICHD has headed an effort to coordinate the development of measures for fatherhood studies, greatly enhancing the comparability and value of the studies being conducted.

NICHD expects to make its first awards in FY 2001 under an innovative program of research on the development of poor children. NICHD has led an inter-agency collaborative initiative, The Science and Ecology of Early Development (SEED), that will support interdisciplinary teams of scientists in studies to examine how economic, social, and neighborhood disadvantage influences the social, emotional, and cognitive development of children. In another collaborative effort, NICHD is teaming with the DHHS Office of Population Affairs and the Centers for Disease Control and Prevention to develop research that will directly translate to action at the program, individual, and societal levels to reduce levels of unintended pregnancy.

Research on health disparities was the focus of a concerted strategic planning effort by the NICHD this year. Building on previous investments in discipline-specific research on infant mortality, child health, and reproductive health, the published plan calls for interdisciplinary research that integrates concepts and methods from the biomedical, behavioral, demographic, and social sciences. The breadth of scientific expertise among NICHD staff and previous experience in supporting interdisciplinary programs of research ideally positions the Institute to seek and identify the complex pathways that contribute to disparities in health status among racial and ethnic groups. Part of this challenge is achieving an improved understanding of our country's racial and ethnic diversity, and the ways in which race and ethnicity influence health. Demographic research is contributing to this task, both through studies of immigrant assimilation and health, and through research on mixed-race adolescents, who have been found to be at high risk for problem behaviors.

NICHD took a major step towards improving information on immigration to the United States during FY 2000. The New Immigrant Study, a large longitudinal study of new legal immigrants, was funded by NICHD with help from the U. S. Immigration and Naturalization Service, the National Science Foundation, the National Institute on Aging, the NIH Office of Behavioral and Social Sciences Research, and the DHHS Office of the Assistant Secretary of Planning and Evaluation. This ground-breaking study will produce information on the health, economic well-being, adaptation, and family circumstances of legal immigrants and their children over a four-year period. Using highly influential demographic models developed for migration between Mexico [and several South American countries] and the United States, other NICHD studies of

immigration and migrant health continue to make important contributions, including a new study examining causes of immigration--both legal and illegal--from China.

NICHD continues to give high priority to planning for the future development of demographic research, including training and infrastructure support. The Institute will conduct long-range planning for demographic research in Fiscal Year 2001. It will also expand its Career Development Award program (K01) to include mentored research and interdisciplinary training opportunities for newly trained demographers. It continues to fund a strong program of institutional and individual training grants in demography. The newly launched Population Research Infrastructure Program (R24) will award its first grants to support cutting-edge centers of demographic research in fiscal year 2001.

Item

Diabetes - The Committee urges NICHD to enhance its research efforts in the area of diabetes, including areas of research highlighted in the Diabetes Research Working Group Report. The Committee also urges NICHD, in collaboration with NIAID and NIDDK, to enhance its efforts to develop a vaccine to prevent juvenile, or Type 1, diabetes and in collaboration with NIDDK and NHGRI to enhance its effort to identify the genes associated with juvenile, or Type 1, diabetes. The Committee requests that the Director be prepared to testify at the fiscal year 2002 appropriations hearing on the steps being taking to increase its support in this area. (p. 76)

Action taken or to be taken

The NICHD has focused its efforts on the earliest pathogenesis of Type 1 diabetes and on optimizing insulin therapy in children with Type 1 diabetes. The NICHD has also initiated more research on the origins of Type 2 diabetes in children and on gestational diabetes mellitus in pregnant women as recommended in the Diabetes Research Working Group Report.

Although grant applications designed to study the pathogenesis and treatment of diabetes have historically been assigned the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) for funding, the NICHD has combined forces with the NIDDK to fund more research on type 1 diabetes in major targeted efforts. For example, in FY 2000 the NICHD set aside $500,000 to join a Program Announcement with the NIDDK to fund new grants designed to study the development of the endocrine pancreas. In FY 2000 the NICHD also contributed $500,000 to extend funding of the type 1 Diabetes Prevention Trial (DPT-1), now in its seventh year. This important trial designed to prevent or delay the onset of diabetes in high risk children (DPT-1) is co-supported by the NIDDK, the NIAID, and the NICHD.

In order to respond to ongoing Congressional interest in this important area of public health, in FY 2001 the NICHD will continue to collaborate with the NIDDK and the NIAID in seeking to develop a Network of 20 centers to perform clinical trials of new immunomodulatory agents to treat or prevent type 1 diabetes. The NICHD will also join the NIDDK and the NIAID in funding four centers of excellence in immunology research to develop vaccines and other new immunomodulatory agents designed to treat, delay or prevent type 1 diabetes. The NICHD will

set aside $2,000,000 in FY 2001 to fund these important joint efforts. Funding will continue at this level through FY 2005.

The NICHD has also initiated a program with the Juvenile Diabetes Research Foundation (JDRF) to cofund grants of mutual interest on Type 1 diabetes research. The first grant to be cofunded is that of Dr. Jin-Xiong She at the University of Florida in Gainesville. He is applying state-of-the-art molecular technology to detect the earliest markers for the immune attack against the β cell in 12,000 infants. The infants will be stratified by five levels of risk according to HLA type and family history of diabetes. DNA chip microarray technology will be used to study differential expression of genes involved in the immunopathogenesis of Type 1 diabetes. The JDF will provide $450,000 in funds over the three-year study, and the NICHD will provide $1,200,000 in total costs over three years.

The NICHD has also initiated a clinical research study entitled "Tolerability and Pharmacokinetics of Inhaled Insulin in Children 6-11 Years of Age with Type 1 Diabetes." Up to 36 units of insulin per day can be delivered through the airway system of the lungs. If inhaled insulin can be shown to be as efficacious as insulin injected subcutaneously, a great milestone in the history of the treatment of diabetes will have been attained. Then the issues of fear of injections and children's compliance with intensive insulin therapy could recede into the past.

The NICHD recently joined the NIDDK in cosponsoring a RFA entitled "Type 2 Diabetes in the Pediatric Population." This important initiative is designed to ascertain the causes for the startling increase in prevalence of Type 2 diabetes in children and adolescents. Preliminary data indicate a fourfold increase of this disorder within the past decade. Studies are needed urgently to ascertain the true prevalence of the problem and to develop predictive markers for the disorder children prior to its onset. The NICHD will contribute $500,000 per year to this initiative in FY 2000-2004.

The NICHD has initiated a 16-site 5-year prospective international study of hyperglycemia and adverse pregnancy outcomes. This study of gestational diabetes mellitus will enroll 25,000 women early in their pregnancy and will follow them through their gestation, delivery, and post-partum period. Their infants will be studied as well. The NICHD will provide $9,420,000 and the NIDDK will provide $1,250,000 to cofund this major initiative, which the largest study of gestational diabetes ever undertaken.

The NICHD, NIDDK, NIA and NIEHS recently cosponsored an RFA on Fetal Origins of Adult Disease in order to uncover the earliest antecedents of Type 2 diabetes and the molecular events that accrue from the interaction of the fetal genetic background with the intrauterine environment to begin the disease process. A total of $3.8 million of grant support will be devoted to this effort each year from FY 2001-2005.

In FY 2001 the NICHD will fund a large clinical trial designed to ascertain how to implement effectively the principles of the Diabetes Control and Complications Trial (DCCT) in children with Type 1 diabetes in an effort to improve glucose control and reduce the complications of disease. Of the 1,441 patients in the DCCT only 195 were adolescents. None were children. The incidence of hypoglycemia in the adolescents assigned to intensive insulin therapy was three

times that of the adults. The important issues of compliance, control, hypoglycemia, and prevention of complications need urgently to be addressed in a pediatric population. This trial will use subcutaneous glucose sensors to monitor levels of blood glucose 24 hours a day. Funding for the first two years of the study will be provided by the Special Appropriation for Diabetes of the Budget Agreement Act of 1997. The NICHD will provide $1 million each year in FY 2003-2005.

Item

E. coli:0157 - The Committee is pleased that NICHD research is yielding and testing a vaccine for the deadly food borne bacterium E.coli:0157. The Committee understands that the Institute is now seeking to determine whether the vaccine is best administered to livestock or to children and others who are most vulnerable to catastrophic food poisoning caused by the bacterium. The Committee urges NICHD to continue this research. (p. 76)

Action taken or to be taken

The NICHD's Laboratory of Developmental and Molecular Immunity (LDMI) is studying the prevention and therapy of infection with *Escherichia coli* O157 and related organisms in 4 areas:

1) The LDMI has been developing conjugate vaccines composed of the purified and non-toxic outer polysaccharide coat of *E. coli* O157 chemically bound to a protein. This type of vaccine, first developed by LDMI for *Haemophilus influenzae* type b, is designed to elicit antibodies that inactivate the inoculum of bacteria as they enter the intestine. Phase 1 trials of *E. coli* O157 conjugates in adults showed the investigational vaccine to be safe and to elicit high levels of antibodies in 100% of the recipients of long duration. Unexpectedly, 80% of the adults responded with a significant rise of antibodies as soon as one week following injection indicating their usefulness in an outbreak. Phase 2 trials in children will begin in January;
2) Preliminary studies of the safety and ability to elicit antibodies in calves for investigational *E. coli* O157 vaccines are now completed. One injection of our polysaccharide-based vaccine induced high and long-lived antibodies in all recipients (about 100 calves). Trials to evaluate the effect on colonization of cattle with this easy-to-administer and inexpensive vaccine are currently being planned;
3) *E. coli* O157 and other *E. coli* have a toxin denoted as *Shigella* toxin. *Shigella* toxin is invariably associated with the hemolytic uremic syndrome, a serious complication that results in death or kidney dysfunction. Once the symptoms of infection with these pathogens become manifest, administration of antibiotics has no effect upon the course of the disease. Accordingly, LDMI is developing methods for large scale production of this toxin in order to prepare hyperimmune globulin with high levels of antitoxin for treatment of hemolytic uremic syndrome;
4) Intramural scientists have also been developing a synthetic vaccine against *S. dysenteriae* type 1, an organism that causes a disease that is very similar to that caused by *E. Coli*. Preliminary experiments in mice show that this synthetic vaccine is significantly more immunogenic that the conjugate prepared with the natural products. Clinical trials to demonstrate efficacy of this radically new product are being sought in developing countries.

Item

Family Literacy Research - For years the Committee has been at the forefront of support for the significant accomplishments of the Institute's extensive program of research on the development of reading skills, identifying and addressing reading difficulties, and strengthening reading instruction, especially for children. The success of this work with children has focused attention on the importance of the ability of parents to assist and support the efforts to teach their children to read effectively. Building on NICHD's research expertise with children, the Committee urges the Institute to work with the National Institute for Literacy to strengthen and expand research-based adult literacy instructional activities and to assist in the dissemination of this information to adult literacy programs across the country. (p. 76)

Action taken or to be taken

The NICHD has formed a partnership with the National Institute for Literacy (NIFL) and the Department of Education, to disseminate information on reading research and instructional practices based on that research. The initial activity of this partnership has been the dissemination of the findings of the National Reading Panel. However, through this partnership and the ongoing cooperation and interaction between the NICHD and NIFL, adult literacy is also being addressed. These activities are in the preliminary stages. NICHD staff have held informal meetings with NIFL staff, and have formally participated in the October, 2000, “Reading Research Working Group Meeting” in Boston, at which an NICHD staff member delivered an address on the applicability of some of NICHD’s longitudinal reading research to adult basic education and literacy.

In addition, in October, 2000, the NICHD and the National Institute on Aging jointly published a program announcement, Age-Related Changes in Reading and Oral Language Comprehension (PA 01-002), which is aimed in part an encouraging applications that would address adult literacy issues related to ability for employment, the accessing of health care, reading instructions required for daily functioning, etc.

Finally, to address the issues of early childhood and family literacy, the NICHD formed a collaboration with the National Institute for Deafness and Other Communicative Disorders, the NIH Office of the Director’s Office of Behavioral and Social Sciences Research, three components of the Department of Education, and the American Speech-Language and Hearing Association. This group sponsored a workshop in September, 2000, on Emergent and Early Literacy, addressing the issues relevant to the development of the precursors to literacy and the earliest literacy, normally appearing in the preschool years and enhanced by parent-child literacy interactions in the home and adult-child literacy interactions in the preschool and other child care settings. The workshop focused on identification, prevention and intervention of early literacy problems, and on parent/adult education and the importance of assisting non-literate or low-literate adults in successful early literacy activities with their children. Workshop members forged a research agenda which the funding partners (NIH and the Department of Education) will consider for future research initiatives.

Item

Fragile X - Fragile X is the most common inherited cause of mental retardation. Most children with Fragile X require a lifetime of special care at immense expense and comprise a homogeneous study population for advancing understanding of these disorders. The Committee encourages NICHD to enhance its research efforts on Fragile X through all available mechanisms, as appropriate, including a consensus conference. The Committee urges NICHD to collaborate its efforts with NINDS and NIMH. (p. 76/77)

Action taken or to be taken

In April 2000 an RFA (HD-00-015) entitled "Neurobiology and Genetics of Fragile X Syndrome" was released. This RFA solicited applications for either small, short term, innovative pilot research grants or larger, longer term, established investigator initiated research grants to address topics of interest that had been established by the participants at the "Workshop in Fragile X: New Research Directions" in 1998. At least $1.2 million in total direct costs was committed for five years and $1.4 million for the first two years by the NICHD, NIMH, and Fragile X Research Foundation (FRAXA) to fund 6 to 8 new grants in response to this RFA. The large number of applications submitted in response to the RFA indicate considerable enthusiasm by new investigators as well as by previously established investigators conducting research relevant to this RFA's scope. The first awards are anticipated in April 2001. A consensus conference in year 2002 or 2003 will be considered following the outcome of proposals funded under this RFA.

The NICHD has also encouraged the Pediatric Pharmacology Research Units (PPRUs) Network to expand its scope to include psychopharmacology clinical trials which could admit individuals with Fragile X in the PPRUs.

Item

Literacy Screening Tool - The Committee commends NICHD for its priority on reading development as a means to better predict reading difficulties, reading disabilities, and learning disabilities in children. The Committee encourages NICHD to continue its collaborative work with the National Center for Learning Disabilities to develop a research-based, literacy-screening tool to identify preschool children at risk for reading difficulty. (p. 76)

Action taken or to be taken

The NICHD has held several meetings with the National Center for Learning Disabilities and NICHD-supported literacy researchers to develop the basic protocol for the development of the preschool literacy screening test. This effort now involves NICHD supported scientists from Florida State University, the State University of New York, The University of Texas Medical School, and program staff at the NICHD. In addition, the Reading Research Program at the NICHD has recently developed an initiative to conduct longitudinal, developmental studies to identify the most powerful predictors of reading success and failure beginning at age three. The

information obtained from this initiative will also be employed in the development of the literacy screening tool.

Item

Maternal-Fetal Medicine - The Committee encourages NICHD to enhance its research efforts into such areas as prematurity, preterm labor, preeclampsia, amniotic fluid embolism, in utero screening for birth defects, post-partum hemorrhage, and other complications related to pregnancy through all available mechanisms, as appropriate, including sponsoring a planning workshop to define research questions and promote collaboration with centers not currently participating in cooperative agreements with the Institute. The Director should be prepared to testify on the progress in this area at the fiscal year 2002 appropriations hearing. (p. 77)

Action taken or to be taken

The NICHD actively sponsors workshops in order to effectively define areas of required research. Planning workshops scheduled for FY 2001 include *Setting a Research Agenda for Stillbirth, Biology of Early Human Placentation and Its Relation to Pregnancy Outcome, Pathogenesis of Poor Pregnancy Outcome from Prenatal Alcohol Exposure* and *Content and Conduct of Follow-up of Very Low Birthweight Infants.* The workshop on *Setting a Research Agenda for Stillbirth* will focus on a much neglected area in obstetrics. Currently there is no significant funding ongoing for research into the etiology and/or pathogenesis of stillbirth. The workshop on *Biology of Early Human Placentation and its Relation to Pregnancy Outcome* will focus on early determinants of pregnancy conditions. It is theorized that the initiation of many pregnancy conditions (including prematurity, preterm labor, preeclampsia) occurs very early in pregnancy, at the time when the embryo implants into the uterus. This workshop will define the research questions focused early in pregnancy with associated pregnancy complications. An additional informal workshop is planned which will focus on genetics of prematurity and low birth weight babies, targeting racial/ethnic populations. Certain racial and ethnic populations have a disproportionate, higher incidence of premature and low birth weight babies. The purpose of this workshop will be to discuss the role of genetics as a component of this health disparity. The results of this workshop will be used as a guide in formulating a RFA for FY 2002. As a result of these planned conferences, recommendations for future research emphasis are anticipated. These recommendations will aid the NICHD in planning and fostering the submission of research proposals that will help lead to more accurate diagnosis and appropriate treatment for these complications of pregnancy.

The NICHD recognizes that amniotic fluid embolism, while a rare maternal complication, is associated with a high rate of maternal mortality, and encourages meritorious, investigator-initiated, research proposals to address this important problem. In response for the need to establish non-invasive procedures to detect birth defects the NICHD has initiated a prospective multicenter clinical evaluation for prenatal diagnosis called the National Institute of Child Health and Human Development Fetal Cell Isolation Study (NIFTY) . The primary goal of this on-going study is to utilize and compare state of the art separation techniques for the isolation of fetal cells from maternal blood for the analysis of chromosomal abnormalities. In reply to another serious maternal complication, the NICHD, the Centers for Disease Control and Prevention and the World Health Organization held a conference entitled “Postpartum Hemorrhage and Placenta Accreta” in February 1999. The participants examined the current body of scientific knowledge regarding these conditions, including the physiology and pharmacological management of the

latter stage of labor as well as surgical techniques for addressing certain cases of postpartum hemorrhage. As a result of the conference, several recommendations for future research were developed, and the NICHD encourages investigator-initiated applications that address the recommended areas of research proposed by this conference.

To ensure that all women can have healthy pregnancies that result in the birth of healthy infants, the NICHD supports basic, clinical, and translational research aimed at preventing and treating those conditions that can adversely influence pregnancy and infant outcomes. Two of the Institute's many successful research programs in this area are the establishment of the Maternal Fetal Medicine Unit (MFMU) Network and the Neonatal Research Network. Since their inception in 1986, these networks have provided the expertise and infrastructure for well-designed clinical trials in obstetrical and neonatal management. These networks consist of centers, which are funded by cooperative agreements, and are recompeted every 5 years. This competitive mechanism allows the Institute to encourage and include other centers of excellence in these programs.

In response to an RFA, issued for the MFMU, a collaborative network of high-risk obstetrical units, a significant number of proposals were received. Their review and funding are taking place in the current year. The MFMU Network is designed to conduct perinatal studies to improve maternal and fetal outcomes. Specifically, the major aims of the MFMU are to reduce the rates of preterm birth, fetal growth abnormalities, neurologic sequelae of the newborn, and maternal complications of pregnancy as well as to evaluate maternal and fetal interventions including efficacy, safety, and cost-effectiveness. Included in these aims are translational research, the use of genetics, and the evaluation of new technologies in the promotion of maternal-child health/prevention of disease. The emphasis is in supporting multi-center randomized, controlled trials.

In addition, a RFA has been issued for *Health Disparity in Preterm Birth: the Role of Infectious and Inflammatory Processes.* This RFA is to determine the role of infectious and inflammatory processes leading to preterm birth and adverse neonatal outcomes in different ethnic populations. The research proposed in response to this solicitation will involve multidisciplinary investigations to clarify the potential role of infectious diseases and the associated immune response as a cause of early preterm birth and fetal and neonatal morbidity. This RFA is designed as a step in reducing one of the major disparities in health outcomes, one of the NIH's Areas of Emphasis and incorporated in the FY 2001-2006 Department of Health and Human Services Strategic Plan.

Finally, a significant amount of basic research is currently being supported by the NICHD in understanding the physiological and biochemical mechanisms of pregnancy. Pregnancy is a complex and interwoven process involving multiple maternal and fetal components that interact with one another. Thus, understanding the basic mechanisms underlying these processes is essential for the rational design of effective interventions to prevent pregnancy related conditions. Areas of basic research include studies on the placenta, uterus, and fetus. The NICHD also supports a number of studies that are examining the events that trigger adverse maternal outcomes such as preeclampsia, placenta accreta, and related disorders.

Item

Mathematical Skills Improvement - The Committee is pleased to learn that NICHD is developing a research initiative on the development of skills needed to learn math, the means to address difficulties learning math, as well as the effective instruction for math. The Committee encourages NICHD to enhance its research efforts in this area. (p. 77)

Action taken or to be taken

NICHD is currently involved in a number of initiatives to foster this program of research. A research conference on Mathematics Development and Cognition was held and the proceedings of that meeting are being used in the development of a specific RFA to solicit grant proposals to better understand normal development in mathematics, mathematics disabilities, and mathematics instruction. In addition, the NICHD is working closely with NSF and OERI within the context of the Interagency Educational Research Initiative and has completed two grant funding cycles to date. Seven research projects are now underway to identify effective instructional approaches for the teaching of different mathematics abilities and skills and to better understand how to translate the results of these studies into practice at the classroom level.

Item

Mental Retardation/Developmental Disabilities - Nearly 500,000 children are born each year in the United States with mental retardation and/or other developmental disabilities. In the past, the Committee has highlighted the importance of research in specific conditions such as Rett syndrome, autism, spina bifida, learning disabilities, and other related diseases. As a result of center-based research focusing specifically on mental retardation and developmental disabilities the knowledge base has been advanced in such areas as imaging technology, the role of experience and genes in brain development, genetic mapping, low birthweight and prematurity, and family functioning. The Committee encourages NICHD to enhance the efforts of these centers to continue the advancement of both basic and clinical research into the causes, diagnosis, early detection, prevention, and treatment of mental retardation and developmental disabilities. (p. 77)

Action taken or to be taken

Research on mental retardation and developmental disabilities has always been a very important priority to the NICHD. Advances and ongoing research in the areas of imaging technology, the role of experience and genes in brain development, genetic mapping, low birthweight and prematurity, and family functioning are highlighted below.

Imaging Technology

The Mental Retardation and Developmental Disabilities (MRDD) Branch of NICHD has supported resources for projects involving various neuroimaging components which have been and are being used in studies of brain structure and function in individuals with a number of MRDD related syndromes: Williams, Down, Smith-Magenis, Fragile X, Rett, and Velo-Cardio-Facial, as well as single gene disorders such as the adrenoleukodystrophies and

Neurofibromatosis Type 1. Studies visualizing gene expression and neural activity in real time in rodents, supported by the MRDD Branch, are complemented by quantification by positron emission tomography (PET), fMRI, and autoradiography.

The Role of Experience and Genes in Brain Development
A number of longitudinal studies are now being conducted in children with various syndromes associated with MRDD to quantify brain function and gene expression during the developmental process. Many of these studies have only been initiated in the past three years and have yet to provide substantive research results, but preliminary data provided in progress reports are not only very exciting, but are providing prospective information about the time of onset of neuropathologic features associated with various syndromes. For example, studies have shown that cognitive and motor development in children with Down syndrome are atypical during the first year of life and that infants, toddlers, and preschoolers with Fragile X syndrome have early neurocognitive alterations in attention, social gaze, visual recognition memory, and sequential information processing.

Genetic Mapping
This has been an exciting year for not only genetic mapping studies relevant to MRDD conditions, but for the entire human genome project as well. The MRDD Branch continues to support mapping studies involving 15 of the 22 human autosomes, the X chromosome, and mitochondrial DNA. Further insight into the genetic basis of the following syndromes (among many conditions) has been obtained by MRDD researchers this year: Rett, Down, Prader-Willi, Angelman, Smith-Magenis, Langer Giedion, and Velo-Cardio-Facial.

Genetic analysis studies in Fragile X syndrome carrier females have provided further insight mechanisms of premature ovarian failure and of increased incidence of chromosomal abnormalities, such as Down Syndrome, among their offspring.

Low Birth Weight and Prematurity
Specific parenting interventions that target preterm infants' specific attention and organization deficits for these infants have been compared with a standard, nonspecific follow-up program. Of particular interest has been an intervention that targets these attentional and organization problems and the extent to which it enhances very low birth weight (VLBW) infants' development when compared with that of full term (FT) infants. Maintaining and redirecting their infants' attention and the use of provision of information and responding contingently to infants' signals may be influenced by maternal factors, such as parenting beliefs, stressful life events, social support and psychological stress. Videotaping sessions with an examiner allow study during exploratory play and social competence situations, with the mother during an every day activity, toy play, and feeding, and the ability of the mother to teach an alternate care giver the parenting intervention skills.

Family Functioning
Longitudinal studies of adjustments in families rearing children with developmental disabilities have now progressed to the assessment of families with children entering adulthood. One study uses a unique set of families that have knowingly adopted children with developmental disabilities, as well as more typical families with birth children with developmental disabilities.

In these families, parent and family characteristics that operated at an earlier time must adjust to the increased demands and strains that the transition to adulthood brings. Stable and enduring factors, such as personality traits and religious beliefs help to predict how well parents will cope with the transition to adulthood of their children with developmental disabilities. Further, observing how adoptive and birth families interact in at-home situations helps better assess how family members affect one another.

Other studies involving family interactions focus on stress in families of young children with various syndromes, including Down, Williams, and Smith-Magenis. Other families with children at risk for both biological and socio-environmental risks for impaired development of arousal and attention, particularly children who have been exposed prenatally to stimulants, like cocaine, have shown that these children are more susceptible to stress factors and are more vulnerable to their detrimental effects.

Facilitation of social outcomes has also been examined in groups of school aged children with mild to moderate MR, including Down syndrome and non-Down syndrome children with learning disabilities. As with all children, the quality of family interactions influences children's social skills and behavioral adjustment, which in turn affect peer relationships and other social outcomes. Direct family member efforts to arrange and monitor social encounters for the children help increase the children's social participation and thus provide experiences that improve social skills. For children with disabilities, both family interactions and the manner in which family members help children cope with social rejection influence the children's ability to process social information and solve social problems.

MRDD Centers

The MRDD Branch currently supports 15 Mental Retardation and Developmental Disabilities Research Centers located throughout the country. Existing centers must recompete for continued funding with new centers, several of which have come into existence in the past five years. This year five centers, four existing, and one proposed new center, will be competing for funds to provide core services to investigators who are supported by a variety of funding organizations, including federal and private agencies. The number of grants accessing these cores which are supported by NICHD and specifically by the MRDD Branch of NICHD has increased substantially over the past five years.

Item

National Center for Medical Rehabilitation Research - The Center is responsible for basic and clinical research dealing with the causes of physical disability and medical rehabilitation interventions to reduce disability and improve the quality of life for persons with disabilities. Congenital limb deficiency, vascular disease, childhood skeletal malignancy and trauma contribute to the over 1.5 million in the U.S. with limb loss. Technological advancements today offer considerable opportunity for persons with limb loss to effectively resume active, productive lives, but standards of care for persons with limb loss have not been developed, nor have clinical outcomes research been conducted to determine appropriate access to advanced technologies and the importance of related physical rehabilitation and therapy to improve

performance among persons who utilize prosthetic devices. The Committee urges NICHD to enhance research efforts in this area through all available mechanisms, as appropriate, including a consensus conference. The Committee also urges NICHD to support the development and distribution of patient oriented information and guidance materials in collaboration with CDC. (p. 77)

Action taken or to be taken

The NICHD has made a substantial investment in research related to prosthetic devices. From 1992 through FY 1999 the National Center for Medical Rehabilitation Research (NCMRR) funded $13,544,000 on research projects related to this area. Funding in FY 1999 alone for prosthetic research totaled $2,278,000. A list of research project titles funded in FY 1999 includes:

- Neuromuscular reorganization for prosthesis control
- Chronic pain management in amputation
- Long-acting opioids in amputation pain management
- Logic controlled electromechanical free knee orthosis
- Interface mechanics, materials, and tissue response
- Externally powered prosthetic hand and wrist
- Dyvascular amputees: rehabilitation use and outcomes
- Biomimetic controller for a multifinger prosthesis
- In-shoe multisensory data acquisition and analysis
- Visualizing diabetic feet to optimize orthotic fitting
- Artificial hand for limb deficient children 2-8 yrs old
- Rolling joint prosthetic leg
- Gyroscope for use in prostheses for standing and walking

In addition, NCMRR organized a Trans-NIH Symposium on Mobility in January 2001. Prosthetics was a major topic in this symposium. NCMRR has also supported the development of an innovative virtual family mentoring system implemented on CD-ROM for use with individuals with limb loss.

Item

National Center for Medical Rehabilitation Research - The Committee encourages the National Center for Medical Rehabilitation Research to continue its work in clinical trials to test the efficacy of medical rehabilitation techniques for stroke rehabilitation and a clinical trial network for brain injury research; regeneration of nerve and skin cells damaged from trauma, including ``tissue engineering'' for amputees and neuron growth related to stroke or spinal cord injury; and medical rehabilitation interventions for the treatment of pediatric trauma. The Committee also encourages the Center to research and develop assistance technologies that enhance the function and independence of persons with mobility and other functional limitations. (p. 77/78)

Action taken or to be taken

In addition to new RFAs for an adult traumatic brain injury network, pilot clinical trials in pediatric brain injury and clinical trial planning grants for trials in pediatric rehabilitation, NCMRR has recently published a targeted initiative for innovative therapeutic approaches to rehabilitation. This RFA was successful in generating considerable interest on the part of a wide group of investigators and in securing co-funding from other NIH institutes. NCMRR has funded a large multi-site investigation into the efficacy of constraint therapy for rehabilitation of stroke, as well as two multi-site studies to determine the efficacy of partial body weight suspension and treadmill training for rehabilitation of individuals with spinal cord injury. Fundamental work on the mechanisms of tissue engineering and recovery from injury remains a major interest of the Center. NCMRR continues to fund projects to develop and evaluate assistive technologies including those for mobility, communication and manipulation of the environment. These have included implantable devices for improvement of shoulder function in paralyzed individuals, an assistive device for dining, and a wide variety of efforts in advanced prosthetics and rehabilitation engineering.

Item

Neurofibromatosis - Learning disabilities occur with high frequency in children with Neurofibromatosis (NF). NF1 provides an opportunity to uncover a molecular basis for cognitive impairment and to identify a marker for brain dysfunction. Research in understanding the cognitive deficits of NF1 patients possesses broad application to learning disabilities in the general population. NICHD is encouraged to enhance its NF research portfolio, coordinate its efforts with other Institutes engaged in NF research, and be prepared to report on the status of its NF research at its fiscal year 2002 appropriations hearing. (p. 78)

Action taken or to be taken

NICHD staff participated in a Neurofibromatosis Workshop held on May 4 and 5, 2000 at the NIH. Important issues addressed at this workshop included basic science issues, therapeutics issues, and research strategy issues. Among the science issues deemed of utmost importance were the identification of issues that must be understood to permit the development of more effective therapeutics for NF1-associated learning disorders. The scientific presentations included a discussion of recent elegant studies of the *NF1* gene in the fruit fly. These *Nf1*-deficient flies have subtle behavioral abnormalities in learning and memory, and the researchers are trying to dissect the signaling pathways in the fly that are important for learning and memory. These studies may elucidate the pathways important in NF1 patient learning disabilities. NICHD staff will encourage investigators to prepare and submit research grant applications that specifically address cognition and brain development in children with NF1. NICHD currently funds research or learning disabilities associated with NF, as well as neuroimaging studies that include studies which examine the relationship of “unidentified bright signals” (UBS) found on MRI scans of children with NF1 to neuroimaging abnormalities, such as macrocephaly.

Item

Pediatric Kidney Disease - .... NICHD is encouraged to enhance research on the understanding and treatment of congenital diseases and kidney malformations which lead to chronic renal

failure and end-stage renal disease in children and adolescents, as well as the prevention and treatment of the adverse effects of chronic renal failure on neurologic and physical development in children. (p. 78)

Action taken or to be taken

The NICHD agrees that the developmental origins of pediatric kidney disease comprise an important area of research. The NICHD research program in developmental nephrology focuses on the genetic and molecular mechanisms that are involved in kidney development during embryogenesis. Of particular interest are developmental studies of the renin angiotensin system during fetal life. NICHD-supported investigators have implicated this system in the regulation of kidney growth and of renal blood vessel formation. They are now seeking to learn more about the regulation of this crucial system during fetal life. The ultimate aim of these studies is to apply new findings at the molecular level to clinical problems in pediatric nephrology.

In addition to basic studies of renal development, the NICHD supports intramural research on the origins of immunologlobin A (IGA) nephropathy, which is the most common primary renal glomerular disease of children. Gene-knockout studies in an animal model implicate a deficiency of uteroglobin as the cause of IGA nephropathy. It is now important to ascertain if uteroglobin deficiency also causes IGA nephropathy in children.

To capitalize on research findings in the area of glomerulonephropathy, the NICHD plans to join the NIDDK in a task force on focal segmental glomerulosclerosis. This task force will be charged with reviewing the current state of knowledge about this disorder and with planning a multicenter clinical trial of possible interventions, such as immunomodulatory agents.

Staff of the NICHD look forward to working closely with staff of the Pediatric Nephrology Program of the Division of Kidney, Urologic and Hematologic Disease of the National Institute of Diabetes and Digestive and Kidney Diseases in addressing the research issues presented in the recently published document entitled Research Needs in Pediatric Kidney Disease-2000 and Beyond.

Item

Pelvic Floor Dysfunction and Incontinence **-** The Committee commends NICHD on the progress made in establishing a research effort/portfolio in pelvic floor dysfunction and incontinence. The Committee understands that a workshop has been held in clinical terminology and that two request for applications will be issued this spring to address translational and clinical research, specifically surgical interventions. The Committee urges NICHD to continue this research and collaborate with NIDDK, NIA, and the Office of Research on Women's Health. (p. 78)

Action taken or to be taken

NICHD, in collaboration with the Office of Research on Women’s Health, has embarked on an effort to address basic biomedical research on female pelvic floor structure and function with the

purpose of stimulating research that can contribute to improving the understanding of pelvic floor disorders and their sequelae. In response to recommendations made at the 1998 workshop, emphasis was placed on research that examines normal pelvic floor function and pelvic floor dysfunction, and reduces the burden of these disorders. The eight proposals selected for funding collectively encompass basic, translational, and clinical research approaches to pelvic floor disorders, with patient-oriented research an underlying theme of several of the applications.

Awards were made to projects that focused on gaining insight into the functional and anatomic defects occurring in women with pelvic organ dysfunction and incontinence. Research encompassing the underlying role of hormones, connective tissue aging, parity, childbirth and delivery practice, racial and ethic differences, and animal models useful in evaluating the integrity of the pelvic floor in human studies are emphasized. The long-term objective is designed to coordinate basic science and clinical research and apply them to disorders of the pelvic floor.

The RFA represented the initial step in our strategy to stimulate research in the field and to provide a framework for future research projects. Studies in this under-researched area will provide much needed information on the normal anatomy and physiology that may underlie pelvic floor dysfunction, urinary and anal incontinence.

In addition, during FY 2000 two additional RFAs on Pelvic Floor Disorder were issued which will fund epidemiologic and clinical research on pelvic floor disorders. An RFA on Epidemiologic Research on Pelvic Floor Disorders will fund research that describes the natural history of pelvic floor disorders, associated risk factors, and effectiveness of risk factor modification for primary and secondary prevention of pelvic floor disorders. Another RFA, for a Clinical Trials Network for Female Pelvic Floor Disorders, invites applications from investigators who wish to participate in a multicenter cooperative program to conduct clinical trials investigating pelvic floor disorders, including pelvic organ prolapse, urinary incontinence, and fecal incontinence. In addition to the clinical sites, a data coordinating center will be funded.

Further, NICHD's Women's Reproductive Health Research Career Centers (WRHR) highlighted urogynecology as one of the subspecialty areas and several WRHR scholars have targeted pelvic floor disorders as a research topic.

Item

Primary Immune Deficiency Diseases - The Committee continues to be pleased with the comprehensive commitment that NICHD has demonstrated in addressing primary immunodeficiency diseases. The combination of peer-reviewed research funded in collaboration with non-profit organizations and active participation with the Jeffrey Modell Foundation's national education and awareness campaign show a serious commitment that should be replicated by other Institutes. The Committee encourages NICHD to remain committed to this collaboration. (p. 78)

Action taken or to be taken

The NICHD supports and conducts basic, clinical, and translational research on inherited or primary immunodeficiency diseases. Moreover, the NICHD sponsors educational activities, conferences, symposia, workshops and meetings to increase the awareness of primary immunodeficiency diseases [PI] among the public, family care practitioners, and pediatricians.

This has been a long-term commitment as evidenced by a number of number of activities in recent years dealing with raising awareness regarding PI. For example, in October 1997, the NICHD organized and sponsored a highly successful three-hour nationwide educational television broadcast to health care providers of a symposium on *Approaches to the Diagnosis and Treatment of Primary Immunodeficiency Diseases.* This interactive telecast was co-sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), National Human Genome Research Institute (NHGRI), Jeffrey Modell Foundation (JMF), and American Red Cross. The entire symposium was videotaped and is available to the public and health professionals for educational and awareness programs.

Last year the NICHD collaborated with the JMF to publish and distribute a booklet entitled *PRIMARY IMMUNODEFICIENCY: When The Body's Defenses Are Missing.* It was written to inform and educate the general public and health professionals about primary immunodeficiency diseases. The booklet has been widely distributed and has proven helpful for patients and families affected by primary immunodeficiencies. The objectives of the booklet are to enhance public awareness of the various types of primary immunodeficiency diseases; provide background on the genetic defects responsible for the symptoms; and serve as a useful information resource for seeking professional assistance, treatment, and patient support groups.

In March 2000, the NICHD and NIAID co-sponsored the National Cancer Institute [NCI] meeting on *Advances in the Diagnosis and Treatment of Primary Immunodeficiency Diseases: Risk of Cancer.* Although patients with chronic primary immunodeficiencies appear to be at greater risk for lymphoid cancers and leukemia, the genetic mechanisms and molecular pathogenesis of this interesting relationship have not been systematically studied. As more patients with primary immunodeficiencies survive longer because of improved treatments, their risk for developing lymphoid and blood cell cancers increases later in life. This meeting afforded an opportunity for basic and clinical scientists to examine the relationship of primary immunodeficiency and cancer, and to develop a plan and strategy to address it.

Several other NICHD-sponsored events this year lead up to the initiation on Capitol Hill of a National Awareness Campaign on PI. In order to highlight the importance of primary immunodeficiencies, the NICHD sponsored a State-of-the-Art Plenary Symposium on the *Gene-based Understanding of X-linked Primary Immunodeficiency Disorders* at the May 2000 Pediatric Academic Societies and American Academy of Pediatrics Joint Meeting in Boston, Massachusetts. An outstanding group of world-renowned experts presented the latest advances on the genetics of X-linked primary immunodeficiencies to a large audience of pediatric health professionals.

Most recently in September 2000, the NICHD sponsored a Clinical Center Grand Rounds on *Severe Combined Immunodeficiency (SCID)*, using a "Bench to Bedside" format, at the NIH in Bethesda, Maryland. The purpose was to increase the awareness of this disease among researchers, physicians, and other health professionals as well as provide an update on the recent advances in the diagnosis and treatment of SCID. This event was televised at the NIH and at hospitals and medical centers throughout the United States.

The events mentioned above were a prelude leading to the launch of a national information campaign about PI in September on Capitol Hill. The goal of this campaign is to increase awareness about PI and its warning signs among health professionals and the public to allow better diagnosis and treatment. Prior to this event, Dr. Alexander, Director, NICHD, sent a letter to the 50,000 members of the American Academy of Pediatrics to alert them to the awareness campaign. The Capitol Hill kick-off spotlighted a newly awarded NIAID grant [co-funded with NICHD and NCI] that will address gaps in knowledge about PI, including its prevalence among minority and uninsured populations. This important campaign, spearheaded by the Jeffrey Modell Foundation, is another example of a public-private sponsorship, which includes NICHD, NIAID, NCI, the CDC, the American Red Cross and various industrial groups.

Item

Reading Development - The final report of the National Reading Panel has made a significant contribution by making widely accessible rigorous research-based evidence on reading development, reading difficulties, and reading instruction. The Committee encourages NICHD to lead the effort to get this report disseminated to teachers, school administrators, parents, and educational policymakers throughout the Nation. (p. 78)

Action taken or to be taken

The NICHD has formed a partnership with the National Institute for Literacy (NIFL) and the Department of Education, to disseminate information on reading research and instructional practices based on that research. This activity has taken several forms. In March of 1999, the National Reading Panel, supported by the NICHD, published its report, "Teaching Children to Read." Throughout 2000, the NICHD has continued to support the National Reading Panel members in making public presentations of the findings delineated in that report, and in disseminating the two volume report and accompanying videotape. In addition, NICHD staff have worked with NIFL on the development of a plan of broader dissemination and implementation of the NRP findings. The NICHD has encouraged NIFL to take the lead in these activities, and continues to support this activity. The dissemination and implementation will be undertaken by the partners (NICHD, NIFL and the Department of Education) and will include the continued distribution of NRP materials, as well as the development of materials based on the NRP findings but geared to specific audiences, such as parents, school administrators, business people, and teachers. Specific materials will be developed for the pre-service and in-service professional development of teachers, especially kindergarten and elementary grade school teachers, who are the front line in teaching our nation's children to read. As future high quality research results become available, it is anticipated that this partnership will continue to facilitate

the translation of these research findings into classroom practices and teacher training and support.

Item

Reading Development - The Committee commends NICHD for the leadership contributions it has provided to the Interagency Educational Research Initiative undertaken with the Office of Educational Research, and Improvement (OERI) at the Department of Education, and the National Science Foundation. The Institute is encouraged to continue its participation and leadership in this promising joint effort. (p. 78/79)

Action taken or to be taken

The NICHD is continuing its close collaboration with OERI and NSF in the development and leadership of the IERI. This collaboration is now entering its third year having completed two full grant solicitations and having just issued a third RFA. To date, the IERI has received over 200 scientific applications for review and has supported over 30 major projects and planning grants. Of significance is the level of partnership achieved by NICHD, OERI and NSF in the development and management of this complex research program.

Item

Reading Development - The Committee is pleased to learn of the progress being made in the Spanish-to-English Reading Initiative launched by NICHD and OERI and looks forward to receiving a status report on the research funded by this effort at the fiscal year 2002 appropriations hearing. (p. 79)

Action taken or to be taken

The NICHD and the Department of Education jointly committed $9 million per year for five years and published a RFA in July 1999 to stimulate research in the Development of English Literacy in Spanish-Speaking Children (NIH RFA HD99-012). In response to that RFA, applications were received in November 1999 and underwent peer review at the NICHD in April 2000. Seven awards were made in FY 2000, expending $4.5 million. This important initiative, building on prior NICHD research, will increase the understanding of the specific cognitive, sociocultural and instructional factors and the complex interaction of these factors that promote or impede the development of English reading and writing abilities for Spanish-speaking children.

For management of the RFA, a coordinating committee was formed, and the funding recommendations were made by that committee. Based on peer review scores, discussion observed at the review meeting, and the written critiques of reviewers, the committee determined that seven applications merit funding at this time: two program projects, two R01s, and three R03s. There is a great need for data that can offer solid empirical evidence to teaching approaches that will most effectively enable US language minority children to develop English literacy; these projects, as designed, will begin to provide such data. The NICHD and Department

of Education have formed a Biliteracy Research Network with the investigators of these projects; the Network's first meeting will take place in November, 2000. The goal of the Network is to form inter-project collaborations that will enhance the probability of convergent evidence on the topic and will seek to answer research questions collectively that would be difficult for independent projects to address.

The coordinating committee elected to fund only the most meritorious applications, as indicated by NICHD peer review. There were many applications that were promising but did not meet the rigorous standards of the peer review panels; therefore, regional technical assistance workshops are planned to offer guidance in the development of grant applications in the important area of biliteracy. Future applications on biliteracy research, both for Spanish and other minority languages, will be accepted as part of the NICHD's regular unsolicited research project grant applications program, and the Department of Education will be invited to co-fund meritorious applications, and successful grantees will be invited to join the NICHD-Dept of Education Biliteracy Research Network.

Item

Women's Reproductive Health Research Career Development Centers - The Committee commends NICHD for providing grants to establish a number of Women's Reproductive Health Research Career Development Centers within ob-gyn departments at various universities and hospitals. At these Centers, newly trained ob-gyn clinicians are provided training and support to assist them in pursuing research careers to address problems in women's obstetric and gynecologic health. NICHD is encouraged to expand the Centers program. (p. 79)

Action taken or to be taken

NICHD is pleased to report that as of this writing, 58 Scholars have been appointed to faculty positions in the twenty Women's Reproductive Health Research Career Development (WRHR) Centers nationwide. They are a diverse group from the various subspecialities and emerging areas of obstetrics and gynecology, and are pursuing a broad range of research topics and disciplines. At the 2000 meeting of the Center Directors, plans were discussed for an evaluation of the overall program which is likely to take place in early FY 2002. Included would be the effectiveness of the program in meeting its goals, and an assessment of whether there remain significant unmet needs.

FY 2001 Senate Appropriations Report Language (S. Rpt. 106-293)

Item

National Center for Medical Rehabilitation Research - The Committee encourages the NCMRR to expand its clinical trials network and program to test the efficacy of medical rehabilitation. The Committee believes that additional funds to the NCMRR also could support a pediatric trauma initiative and a new program regarding tissue and cell plasticity and recovery from injury. (p. 130)

Action taken or to be taken

NCMRR has published two RFAs to stimulate research in pediatric rehabilitation. The first is for pilot clinical trials of pharmacologic agents in pediatric traumatic brain injury. This initiative is intended to support pilot trials to demonstrate the safety and efficacy for children of agents used in the adult population for TBI. The second initiative is a clinical trial planning grant for trials in pediatric rehabilitation. These grants are intended to support investigators in the complex task of planning clinical trials for pediatric rehabilitation and preparing grant applications to support these trials. NCMRR will shortly publish an RFA to develop a clinical trials network for adult traumatic brain injury. This large scale network will include acute and rehabilitative care to span the entire course of traumatic brain injury and promote development of clinical trials for treatment of traumatic brain injury.

Item

Pregnancy Complications- The Committee encourages the NICHD to consider sponsoring a planning workshop in fiscal year 2001 for the purpose of defining research questions in such areas as pre-maturity, pre-term labor, pre-eclampsia, amniotic fluid embolism, in utero screening for birth defects, post-partum hemorrhage, and other complications related to pregnancy. (p. 131)

Action taken or to be taken

Please refer to page NICHD-42 of this document under the heading of Maternal- Fetal Medicine for NICHD's response to this significant item.

Item

Autism- Autism is a developmental disability that typically appears during the first 3 years of life. Presently, there is no effective means to prevent the disorder, no fully effective treatment and no cure. The Committee is concerned by reports indicating an alarming rise in the incidence of autism and by the lack of concrete knowledge of the prevalence of this disability. Early intervention is critical for affected children to gain maximum benefit from current therapies but autism is easily misdiagnosed or undiagnosed. The Committee commends the Institute for its work to encourage professional groups to develop a standardized and universal diagnostic criteria

in autism to aid in earlier diagnosis. The Committee is encouraged by the ongoing collaboration of research advocacy groups and the NICHD on the development and implementation of an awareness campaign for health professionals and for parents to learn to recognize and identify the early symptoms of autism. (p. 143)

Action taken or to be taken

In June 1998, the NIH/Autism Coordinating Committee led by NICHD and NINDS convened an interdisciplinary research conference, *Autism: State of the Science in Screening and Diagnosis*. At that meeting, representatives of the major medical academies, other health-related professional organizations, and patient advocacy groups discussed the findings from ten commissioned papers that reviewed more than 2500 published studies on early detection and diagnosis. Research results of that meeting were published in a special issue of the *Journal of Autism and Developmental Disorders* (1999; volume 29, no. 6). The American Academy of Neurology convened a follow- up meeting of representatives of 11 medical academies and other health related professional associations and patient advocacy groups to review those findings and develop the first consensus statement of clinical guidelines for professionals, "Screening and Diagnosis of Autism Spectrum Disorders" published in the journal *Neurology* (2000, vol. 55, pp. 468 – 479). These clinical guidelines were endorsed by representatives of the American Academy of Neurology, the American Academy of Pediatrics, The Child Neurology Society, the American Academy of Audiology, the American Occupational Therapy Association, the American Speech-Language-Hearing Association, the Autism National Committee, Cure Autism Now, the National Alliance for Autism Research, the Society for Developmental Pediatrics, and the American Psychological Association. Last Spring representatives of the patient advocacy groups met with communication and public information officers from the NICHD, the National Institute of Mental Health (NIMH), the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute on Deafness and Other Communication Disorders (NIDCD) to discuss ways to increase public awareness of autism spectrum disorders. Autism websites are now available at NICHD, NIMH, NINDS, and NIDCD linked to the Library of Medicine Medline Plus system to provide accurate and up-to-date information on research in autism. In addition to scholarly publications, this past year NICHD staff contributed to reports on autism in public media such as the New York Times, the Washington Post, USA Today, and other local and regional newspapers, as well as Newsweek magazine, and television programs such as 60 Minutes, and ABC Dateline. Additional public awareness partnering efforts with the patient advocacy groups are being considered

Item

Autism - The Committee is encouraged by the Institute's rapid response to conduct research on the hormone Secretin as a treatment for autism, and is pleased with ongoing research efforts on the genetics of autism. The Committee recognizes the potential of the collaborative programs of excellence in autism, which comprise a network of sites for the conduct of basic and clinical research into the cause, diagnosis, early detection, prevention, control and treatment of autism. The Committee strongly encourages the NICHD to expand this network so that it is fully engaging in comprehensive autism research, including making individuals aware of opportunities to participate as subjects in research. Further, the Committee continues to encourage the NICHD

to coordinate research efforts with the NIMH and other Institutes conducting autism research. (p. 143)

Action taken or to be taken

Since 1997, NICHD, with co-funding from the NIDCD has supported an interdisciplinary research Network on the Neurobiology and Genetics of Autism comprising 10 Collaborative Programs of Excellence in Autism (CPEAs). More than 75 scientists from over 26 universities are engaged in autism research at these sites, linked to an international consortium of additional sites in Europe. Through participation in this international consortium the Network actively collaborates with virtually all NIMH and other NIH-and independently-funded genetics of autism projects.

Each of these multidisciplinary, often multisite projects is studying some particular basic and clinical aspects of the biological etiology (including possible genetic, immunologic, and/or environmental causes), brain structure and function, and clinical course of autism. Each individual CPEA has a unique focus and research plan. In addition, all projects use a common diagnostic protocol and common core measures and procedures to address collectively some research questions that are beyond the resources and/or subjects of any single project. Individually and collectively the CPEAs investigate the causes, diagnosis, early detection, treatment, and ultimately prevention of autism. The CPEAs include expertise ranging from molecular genetics and developmental biology to clinical assessment and developmental pharmacology.

Regular meetings of the Network Steering Committee, an annual scientific meeting of investigators from all projects, and ongoing subcommittee working groups on topics such as genetics, cognitive development, and communication in autism, together with e-mail and telephone conferencing provide for the coordination of information across CPEAs within, and, as appropriate, outside the CPEA Network. Extensive outreach and shared strategies for recruitment and retention, including NICHD and individual CPEA websites make individuals aware of opportunities to participate in CPEA research projects. Currently more than 2000 well-characterized individuals with autism are participating in studies. Ultimately, more than 4500 carefully diagnosed persons with autism for whom genotypic and phenotypic data have been collected will participate. Both competitive and administrative supplements to these projects have expanded the focus of this Network to include such topics as the development of methods in genetics analysis, e.g., quantitative trait analysis, advances in pediatric neuroimaging , e.g., correction of motion errors in brain scan analyses, and neuropsychology, e.g., collaborative CANTAB computer administered neuropsychology test battery analyses. The existence of this Network of CPEAs has also provided an opportunity for rapid turnaround clinical research studies on important issues regarding public health such as evaluation of treatment with the neuropeptide secretin and the possible relationship between MMR vaccination and autism.

In the first three years of its existence, in addition to carrying out its own individual CPEA specific objectives yielding a total of more than 130 publications (plus abstracts), the CPEAs have seven major trans-Network studies completed or in progress. These include collaborative, double-blind, placebo-control studies of treatment with secretin, testing for candidate genes

mutations in developmental genes HoxA and Hox B, language and communication development, executive (brain) function, head circumference and brain development in autism, early cognitive development, and a 12-site case-control study of regression and MMR vaccination in persons with autism and healthy controls.

Item

Autism - The Committee recognizes that research into the genetics of autism is being supported by several Institutes at the NIH. Given the difficulty of recruiting multiplex families, the Committee urges that researchers be strongly encouraged to collaborate and share this important resource and notes that a collaborative autism gene bank is already in existence, the autism genetic resource exchange. To that end, the Committee is encouraged by the efforts of the NIMH to combine data sets and directs that all Institutes conducting autism research participate in that endeavor. (p. 143)

Action taken or to be taken

NICHD, as the leading NIH supporter of genetics of autism research, encourages and supports collaboration among investigators both within the ten NICHD/NIDCD Network on the Neurobiology and Genetics of Autism: Collaborative Programs of Excellence in Autism (CPEAs), and among all NICHD-funded genetics of autism projects and NIMH-, NINDS-, privately - and internationally-funded genetics of autism projects. In March 2000, the NICHD co-funded an international conference that brought together virtually all known autism genetics projects, including the autism genetic resource exchange, to facilitate sharing and stimulate the pace of this research. A follow- up meeting of this international group was held in New York City in October 2000, and several linkage and candidate gene collaborative studies are planned or underway.

Item

Autism - The Committee encourages the interagency autism coordinating committee to continue to meet regularly and encourages annual public participation, including the active involvement of patient advocacy groups. The Committee requests that the Director be prepared to report to Congress on the goals set and progress made regarding autism research during the fiscal year 2001 {sic} hearings. (p. 143)

Action taken or to be taken

The NIH Autism Coordinating Committee has greatly facilitated collaboration on and funding of NIH autism research. Inter-Institute Directors' level meetings, co-chaired by the Director, NICHD, and the Director, NIMH, are held three times a year to coincide with NIH funding periods. At those times, unfunded research projects, scientific gaps in research, and future research plans are discussed. NIH/ACC membership has been expanded beyond the original members – NICHD, NIMH, NINDS, and NIDCD, to include NIAID, NIEHS, and the National Center for Complementary and Alternative Medicine (NCCAM). Liaisons from other federal agencies including CDC, FDA, and the Department of Education attend when relevant topics are

on the agenda. Reports of these meetings are sent to the patient advocacy groups. Annually, the patient advocacy groups participate in an additional Directors' level NIH/ACC meeting where information about currently funded and planned research initiatives is exchanged. Detailed summaries of currently funded research in autism are sent to the patient advocacy groups prior to the annual NIH/ACC advocacy group meeting. Program level staff members from all participating NIH institutes meet monthly to develop new joint initiatives and to carry out initiatives agreed upon at the other NIH/ACC meetings. An annual NIH/ACC collaborative conference is held to address emerging scientific opportunities and new directions in autism research. Patient advocacy groups are invited to provide nominations for topics and speakers for these NIH/ACC conferences and their representatives participate in these conferences and other meetings as appropriate, e.g., NICHD/NIDCD protocol planning meeting for the Autism Regression/Vaccination Study (see below).

The longterm goal for autism research at the NIH is the prevention and cure of the autism spectrum disorders. One goal for autism research in FY 2000 was to continue and expand support for autism specific research, research on related disorders that might inform autism research, and for basic research potentially related to the diagnosis, etiology, pathophysiology, developmental course, and/or treatment of autism. The number of NIH Institutes now involved in autism research and the breadth of that research has been expanded. NIH support for autism spectrum research has increased dramatically from $11.7 million in FY 1994 to over $49.0 million in FY 2000. Further expansion of that research in FY 2001 will be sought through a joint NIH/ACC Program Announcement inviting research in a broad array of areas in autism.

A second goal for FY 2000 was to accelerate clinical research, especially research with implications for treatments in autism. The NICHD expanded its treatment research initiatives in autism by providing supplements to selected NICHD/NIDCD Collaborative Programs of Excellence in Autism (CPEAs) for a multisite, double-blind, placebo-controlled study of the efficacy of secretin in the treatment of autism. With co-funding from the Centers for Disease Control and Prevention (CDC), the NICHD/NIDCD CPEA Network has also initiated a twelve-site clinical study of regression and vaccination in autism (see above for detail). In addition, research such as that sponsored by NINDS that reported biomarkers of autism at birth and by NICHD to identify biomarkers for subgroups in autism in the CPEA Network has been expanded because of the potential of research such as this to contribute to early detection and intervention in autism.

A third goal for FY 2000 was expanding public awareness of autism spectrum disorders and of opportunities to participate in autism relevant research. Communications and Public Information Officers from NIH/ACC Institutes met with patient advocacy groups to discuss strategies for increasing public awareness of autism spectrum disorders research. An Autism specific website at NICHD is now linked to the Library of Medicine Medline Plus system to provide comprehensive information on autism spectrum disorders to researchers, other professionals, family members, and the general public.

A fourth goal for FY 2000 was to facilitate and expand coordination across genetics of autism research projects. NICHD co-sponsored an international Genetics of Autism working meeting that brought together representatives of all NIH-funded genetics of autism research teams, all

known US and international genetics of autism teams actively involved in autism genome research, including the autism genetic resource exchange to facilitate sharing and stimulate the pace of this research. A follow-up meeting of this international group was held in New York City in October 2000, and linkage and candidate gene collaborative studies are planned or underway.

Item

Bone Disease in Adolescents- With the high number of teen pregnancies, it appears to the Committee that more research is needed to understand the relationship between pregnancy and lactation and bone mass in adolescents. In particular, the Institute is requested to address the impact of chronic anticoagulation on bone mass in pregnancy; the effect of oral contraceptives on acquisition of peak bone mass and bone loss in early adolescents; and the impact on bone status of chronic under-nutrition of young women. The Institute is also encouraged to continue the dual focus on people and animal models for the treatment of osteogenesis imperfecta. (p. 143)

Action taken or to be taken

The NICHD is very concerned about bone disease in adolescents, especially the earliest precursors of low bone mineral density. Data from the National Health and Nutrition Examination Survey III show that the mean calcium intake of adolescent girls in this country is 800mg/day rather than the 1300mg/day recommended by the Food and Nutrition Board. In an effort to improve this situation, the NICHD has greatly augmented its support for osteoporosis prevention research. We have come to recognize that osteoporosis, like many other chronic diseases, may have its roots in childhood. Many children enter their adulthood with compromised skeletal systems from poor nutrition and exercise habits. Others have compromised bone mineralization resulting from chronic disease.

NICHD is currently funding 13 grants in the area of osteoporosis prevention, which were initiated in response to two RFAs issued by the Institute in the past three years. As a result of these initiatives, NICHD-funded researchers are studying several thousand children prospectively to assess the effect on bone mineral density of various dietary, exercise and behavioral interventions. Other recent programmatic initiatives include studies of the genetic basis of bone mineral density and acquisition of peak bone mass. The NICHD has also begun an important educational program called Milk Matters to get children to increase their calcium intake. The NIDR and the American Academy of Pediatrics are working with the Institute to achieve this goal.

The Institute has begun to address the issue of anticoagulation during pregnancy and its effect on bone in adolescence. Thromboembolism remains the principal cause of maternal mortality in both the African American and Caucasian populations in the United States. A thrombotic event in pregnancy is treated with heparin for the duration of pregnancy and at least six weeks after delivery. However, treatment with heparin places these women at increased risk for episodes of bleeding as well as osteoporosis. Studies have shown significant demineralization of bone following prophylactic heparin use during pregnancy.

In NICHD's Maternal-Fetal Medicine Unit Network there is an ongoing study entitled A Prospective Observational Study of Effects of Factor V Leiden Mutation on Maternal and Perinatal Outcome. The factor V Leiden mutation is the most common genetic predisposition to thrombosis; however, its relationship to thrombosis in pregnancy is not known. The carrier rate of factor V Leiden is 3-4% in a non-pregnant population. This study will enroll 5000 women and will determine the incidence of pregnancy-related thromboembolism in women carrying the factor V Leiden mutation and the pregnancy-related morbidity and mortality for the mother and her offspring.

The NICHD also shares the Committee's concerns about the relationship between pregnancy and lactation and bone mass in adolescents and is funding a study of calcium kinetics and bone mineral density in a group of pregnant adolescents whose mean age is 16 years. Findings to date indicate a significantly greater calcium absorption and calcium loss during pregnancy than were observed in the same adolescent girls one month after delivery. In regard to the effect of lactation on bone mineral density, a tendency was noted for lactating adolescents to have lower bone mineral density compared to non-lactating adolescents.

The NICHD also shares the Committee's concerns about the effects of contraceptive progestins such as Depo Provera on bone growth in adolescence. The Institute is currently funding four studies on this topic. Results of these studies indicate that Depo Provera slows bone growth during adolescence. Preliminary results indicate that this effect is reversible, and bone growth resumes once ovarian function is reestablished, within six months of the last injection.

The NICHD encourages research focusing on how inherited, environmental and nutritional factors influence bone mineral acquisition during adolescence. We are interested in how these and other factors determine bone size, mass, and integrity. The NICHD intramural program is involved in studies to improve the treatment of osteogenesis imperfecta (OI). A four-arm randomized controlled trial has begun using pamidronate and growth hormone in the treatment of this disorder. Studies are also under way to ascertain the molecular and genetic basis of OI. The NICHD has joined the NIAMS in issuing an RFA on new research strategies in OI. This initiative will support studies in FY 2001-05 designed to explain the mechanisms of skeletal pathology in OI and to develop new therapies for the disorder.

In FY 2001 the NICHD is planning to obtain normal standards for bone mineral density in 1200 children. Our ability to diagnose and treat children with chronic diseases that affect the bone remains limited because the current age-specific norms for bone mineral density are often inaccurate. Standard reference data throughout childhood are a potentially valuable resource for both clinicians and investigators in this field. These data will enhance our ability to diagnose and treat children with low bone mineral density.

Item

Child Development and Behavioral Research- The Committee is pleased that NICHD is undertaking a number of initiatives to increase understanding of the behavioral and cognitive aspects of child development. The Committee encourages these efforts and looks forward to receiving updates on their progress. (p. 144)

Action taken or to be taken

The NICHD supports many highly significant studies that address issues pertaining to children's social, cognitive, emotional, and behavioral development. These studies include research on early perceptual development and attention, memory processes and thinking skills, the development of perspective-taking ability, social competence and self-esteem, and the formation and maintenance of peer relationships during childhood and adolescence. In addition to these studies, a number of projects examine aspects of socio-emotional and personality development that influence behavior in a variety of settings and situations, including the development of shame and empathy, self-regulation, aggressive and prosocial behavior, attachment relationships, and gender-role behavior. NICHD's research programs in this area address a variety of influences on the developing child which include biological, social, emotional, cognitive, cultural, economic, and policy factors. Most studies in these programs address the complex interactions between these factors in explaining child behavior in different contexts and in predicting patterns of risk and resilience among children at different stages of development. Over the past few years, many of these studies have increased our understanding of factors that protect children from harmful influences and promote healthy development, as well as those that place children at risk for poor developmental outcomes. Several of these studies, in turn, have led to new and innovative preventive intervention projects, designed to test the efficacy of new approaches to preventing problems in child development.

In recent years, the NICHD has also undertaken several new initiatives to increase our understanding of cognitive and behavioral development. The Child Development and Behavior Branch, which was established in 1998 to provide maximum programmatic coverage for child development and behavior research, has continued to expand since its inception. In the past two years, the Branch has developed initiatives to better understand how inherited, dispositional, environmental and experiential conditions are integrated in development to mold, moderate, and predict human learning and behavior. Critical to these initiatives has been an emphasis on the development of dynamic research methods and approaches that assess and describe complex behavioral and biological interactions as they unfold over time. Concurrently, the Branch has developed and initiated new lines of research to emphasize and address issues of causality, particularly with respect to the timing, scope, interaction, and impact of well-defined environmental, experiential, neurobiological, and genetic factors on individual differences in cognitive, social, emotional, language, and academic development.

In the past two years, the Child Development and Behavior Branch has also developed new programs in child abuse and neglect and violence, which aim to increase our understanding of the antecedents, consequences, and mediators of the effects of violence on child development. In FY 1999, the NICHD collaborated with other NIH institutes and other federal agencies to issue a RFA for Research on Child Neglect. As a result of this initiative, NICHD is currently funding seven applications which address various aspects of child neglect including: the causes and assessment of child neglect; the impact of child neglect on school adjustment and academic performance in young children; the consequences of neglect for adolescent development, delinquency, and health risk behaviors; the effects of neglect on adult health status and health risk behavior, economic productivity, and use of health services; and the impact of welfare reform and policies on the functioning of low-income, high-risk families. Also in FY 1999,

under the leadership of the Office of Behavioral and Social Sciences Research (OBSSR) at NIH, the NICHD collaborated with other NIH institutes to issue an RFA on Youth Violence Intervention Research. As a result of this initiative, the NICHD is currently funding five applications focusing on different interventions for youth violence including parenting programs, school-based prevention programs, preventive interventions for high-risk adolescents, and the development of measurement tools and techniques. A third trans-NIH initiative begun in FY 1999, is a program announcement designed to encourage the career development of investigators interested in child abuse and neglect research. Currently, the NICHD is funding three applications as a result from this initiative.

The NICHD has also been involved with several other activities related to children's cognitive and behavioral development. During the past two years, the NICHD has organized and conducted three meetings to address issues of definition and classification in child abuse and neglect research that have impeded research progress in this area. The results of these meetings have led to recommendations for a research agenda in this area, which the NICHD is currently developing. The NICHD is also currently participating in a trans-NIH program announcement on basic and translational research on emotion, which is designed to increase our understanding of emotional development and its interactions with cognitive, social, and biological development, as well as of effective applications of basic research. Finally, the Child Development and Behavior Branch and the Demographic and Behavioral Sciences Branch of NICHD recently issued a joint program announcement on the Science and Ecology of Early Childhood Development (SEED). This initiative encourages research on the normative development of children in poverty, including research on physical health, and cognitive, social, affective, and language development and their interactions. SEED is expected to lead to a number of collaborative studies that are multi-disciplinary and that can inform current policy efforts.

Item

Chromosome 18- The Committee is aware of efforts to encourage new scientific work into the molecular genetic, clinical and therapeutic aspects of chromosome abnormalities. Chromosome abnormalities involving chromosome 18q result in growth failure, mental retardation and central nervous system dysmyelination. Very little NIH-funded research has been devoted to studying the abnormalities of chromosome 18, despite the annual presence of report language urging such research. The Committee encourages the Institute to place special emphasis on funding chromosome 18 research applications. (p. 144)

Action taken or to be taken

Please refer to page NICHD-33 of this document for NICHD's response to this significant item regarding Chromosome 18 Research.

Item

Demographic Research- The Committee commends NICHD's aggressive support for research on the causes of demographic trends and their impact on our society. The availability of objective information about such topics as teen childbearing, declining marriage rates, fatherhood, health

disparities, racial and ethnic diversity, and migration within and across our borders remains a high priority. NICHD is encouraged to expand its commitment to the training and development of new demographic scientists and to assure continued support for the research infrastructure that provides the foundation for advances in population research in centers around the nation. The Committee also commends NICHD's many collaborative projects with other Federal agencies--including the Immigration and Naturalization Service, the National Center for Health Statistics, the Department of Education, and others--which have created innovative demographic datasets on topics of critical importance to policy makers. (p. 144)

Action taken or to be taken

Please refer to page NICHD-35 of this document for NICHD's response to this significant item regarding demographic research.

Item

Diabetes- More than 120,000 children suffer from diabetes, making it the second most common chronic disease affecting kids. The Committee is concerned that NICHD has not substantially increased its role in this area and believes that the Institute should support more juvenile diabetes grants. The NICHD is encouraged to work with NIAID and NIDDK on an initiative to create a coordinated international effort to develop a vaccine to prevent juvenile, or Type 1 diabetes. (p. 144)

Action taken or to be taken

Please refer to page NICHD-37 of this document for NICHD's response to this significant item regarding diabetes.

Item

Fragile X- The Committee commends the NICHD for its research activities on Fragile X, the most common inherited cause of mental retardation. Fragile X results from the failure of a single gene to produce a specific protein. Thus, the Committee understands that Fragile X is a `research portal' for other inherited diseases, especially autism, and the Committee urges NICHD to coordinate its research and research funding with other Institutes, especially NIMH and NINDS to pursue the understanding of the functions of the Fragile X protein. The Committee encourages NICHD to consider organizing a Fragile X Consensus Development Conference (CDC) this year and report the results to it as soon as they are available. (p. 144)

Action taken or to be taken

Please refer to page NICHD-41 of this document for NICHD's response to this significant item regarding Fragile X.

Item

Health Behaviors of Youth- The Committee is increasingly concerned about youth and health behaviors and their impact on society as a whole. Issues relative to school violence, school failure, drug and tobacco use and other behavioral issues have become public health priorities. The Committee is pleased that the NICHD will be collaborating with the Centers for Disease Control and Prevention, the Substance Abuse and Mental Health Services Administration, and the Health Resources and Services Administration to develop a collaborative program in this regard. The Committee requests that the agencies involved focus a portion of their efforts on discovering approaches to intervene and prevent complex behavior problems in children and youth which utilize molecular neuroscience, brain mapping, behavioral analysis and behavioral analysis. (p. 145)

Action taken or to be taken

The NICHD shares the nation's concern about the current health and health behaviors of our youth, their impact on society and implications for future health. In 1999, a Request for Applications (RFA) was published encouraging descriptive research on children ages 6-12 years to identify precursors of risky sexual behaviors and to develop effective intervention strategies to prevent early sexual initiation. Three studies are being funded which address the aims of the RFA. One intervention study for late elementary school-aged, urban minority students focuses on the need for improved parent-child communication, for enhanced classroom curriculum, and for service learning, in which youth participate in structured, supervised volunteer work as part of their regular school day. A second intervention study of minority children takes place outside the school and examines the mother's influence on the sexual behavior of her pre-adolescent children. A third study involves a culturally focused, life-skills development program for middle school minority girls and their mothers in an after-school setting. These studies form the core of NICHD research aimed at identifying the precursors of risky sexual behavior in younger children and call for the development, implementation, and evaluation of theory-based interventions. This transfer of science into programs will help to identify good practices for linking research with community operations.

Tobacco use is the single leading preventable cause of death in the United States and is one of the Healthy People 2010 Leading Health Indicators. Smoking in adolescents has increased in recent years and in 1999 more than one-third of all high school students reported smoking on one or more days in the previous 30 days; and nearly 17% reported smoking frequently (on 20 or more days). Numerous studies are currently being funded dealing with a variety of tobacco use related problems. One innovative intervention project aims to prevent the initiation of smoking by young children by changing the smoking-specific socialization of children in households where parents smoke cigarettes. Another study examines nicotine withdrawal symptomatology in adolescents based on gender and the quantity of tobacco used. Testing for cognitive performance deficits and alterations in responsivity to physical and mental stress during nicotine withdrawal may provide valuable information regarding the process of development and maintenance of nicotine dependence. One prospective study of the effects of prenatal tobacco exposure on the offspring of 755 women has identified significant effects on the offsprings' development of the central nervous system and on delinquent behavior and peer problems. This

study will assess the long-term effects of mental and physical development, temperament, psychological status, activity levels, academic performance, behavior problems, the environment, and prenatal exposure on the adolescents' substance use at age 14 and 16. The study will explore the predictors of adolescent tobacco use across time, from birth to adolescence. Another program for 13-17 year old adolescent smokers evaluates the efficacy of pharmacologic intervention (Buproprion) vs Buproprion with brief office intervention and parental support vs placebo and minimal intervention. Identifying effective interventions is the goal of this study. Health disparities are addressed in another smoking intervention study designed for Arab American youths. Project Toward No Tobacco Use (Project TNT) is the intervention designed for this culturally diverse population.

Youth violence, endemic to our society, is a nationally recognized public health problem, with consequences that include severe psychological and social dysfunction as well as injury and death. In order to reduce the overall level of youth violence, RFA 0D-00-005 "Research on the Development of Interventions for Youth Violence" was written with specific aims to interrupt at an early stage, the behavioral trajectories that can lead to serious youth violence, to direct efforts at specific risk and protective factors, and to target the developmental sequences leading to the establishment of stable patterns of violent behavior. NICHD is funding five grants that were submitted in response to this RFA.

Item

Infertility and Contraceptive Research- The Committee continues to place high priority on research to combat infertility and speed the development of improved contraceptives. It urges NICHD to continue aggressive activities in this area, including individual research grants and support through the infertility and contraceptive research centers. (p. 145)

Action taken or to be taken

The cost of treating infertile couples including assisted reproduction now exceeds $3 billion dollars annually. Moreover, despite the recent introduction of new steroid contraceptive options, it is generally agreed that the available methods of fertility control are inadequate to meet the varied and changing personal needs of couples at different times in their reproductive lives. Therefore, the NICHD continues its long-standing commitment of supporting research on contraception and infertility. Indeed, the NICHD Strategic Plan 2000 entitled "From Cells to Selves" has identified Reproductive Health for the 21st Century as one of its four major areas for initiative development and expansion. The NICHD has proposed eight goals to address needed research in the area of reproductive health including the use of genetic advances to identify factors leading to infertility and novel contraceptive leads, the identification of novel treatments for common reproductive problems, and the identification of new strategies for improving contraceptive use.

Major efforts in infertility and contraception research continue to be made through the support of three Contraceptive Development Centers and two Infertility Research Centers. A major focus of the Contraceptive Development Centers is on contraceptive vaccine development, while the Infertility Centers continue to focus primarily on female infertility. In fiscal year 2001, the

NICHD will announce the recompetition of both the contraceptive development and infertility research center programs through a Request for Applications (RFA). In addition to these five centers, the NICHD continues to utilize investigator-initiated grants, cooperative agreements and the contracting mechanism to fund research related to contraception and infertility. In this regard, three programs are worthy of mention. First, the Contraceptive Clinical Trials Network, which consists of nine sites around the country, has completed Phase I trials of three spermicides, and is undertaking a Phase II clinical study of a progesterone receptor modulator for efficacy as an emergency contraceptive. Secondly, the Reproductive Medicine Network, a national network of nine sites, has recently completed a clinical trial on the analysis of semen in infertile men, and is currently conducting a clinical trial to study the effectiveness of endometrial biopsies in the evaluation of infertile women. Finally, bench-to-bedside translational research in reproduction is supported by the NICHD through a national network of 14 centers as part of the Specialized Cooperative Centers Program in Reproduction Research (SCCPRR). Research supported through the SCCPRR currently includes preclinical testing of a novel female contraceptive, efforts to improve assisted reproductive technologies, and basic and clinical studies to address infertility-related diseases and disorders such as androgen-insensitivity syndrome, polycystic ovarian syndrome, premature ovarian failure, endometriosis and idiopathic hypothalamic hypogonadism.

Item

Learning Disabilities in Infants and Children- The Committee urges research on the outcome and effectiveness of primary and preventive health care for mothers to prevent learning disabilities in infants and children. (p. 145)

Action taken or to be taken

Several maternal and pregnancy related factors are known to be associated with learning disabilities in infants and children. Extreme prematurity and delivery of very low birth weight babies is one such factor which is being investigated with respect to deleterious biological, cognitive and behavioral outcomes. For example, one ongoing investigation is examining the effects of the initiation of labor and the prevention of prematurity on cognitive and behavioral development. There are also several studies examining the long-term physical and cognitive outcome of very low birthweight (VLBW) babies and documenting neurologic and intellectual dysfunction found in this cohort. Another study has been supported to obtain pilot data for a prospective longitudinal study to investigate, using quantitative noninvasive tools, the growth and neurodevelopmental outcomes of infants of preeclamptic mothers.

The role of prenatal factors, particularly diet, in outcomes associated with pregnancy and infancy is the focus of several studies funded by NICHD. One prospective study of maternal growth during adolescent pregnancy is being conducted to identify variations in growth patterns and potential behavioral and cognitive sequelae that may influence learning. This study may also help explain the ethnic differences in birthweight and the long-term consequences of adolescent pregnancy. Another interesting study examines the social and psychological factors that precipitate various school-related delays in children of teenage mothers. The central focus is on

tracing and predicting children's intellectual, emotional, and social development based on maternal, child, and social-environmental characteristics.

Intrauterine exposure to alcohol may lead to Fetal Alcohol Syndrome (FAS) or to Alcohol-Related Neurodevelopmental Disorder (ARND). The NICHD is working with the Interagency Coordinating Committee on Fetal Alcohol Syndrome to identify areas for future research initiatives, including preventive measures for pregnant women and improved neurodevelopmental assessment tools to aid in the diagnosis.

Item

Maternal-Fetal Medicine -The Committee urges the NICHD to coordinate a planning workshop in fiscal year 2001 for the purpose of defining research questions in such areas as pre-maturity, pre-term labor, pre-eclampsia, amniotic fluid embolism, in utero screening for birth defects, post-partum hemorrhage, and other complications related to pregnancy. The outcome should provide the basis for the development of appropriate funding mechanisms to implement the recommendations of the workshop. (p. 145)

Action taken or to be taken

Please refer to page NICHD- 42 of this document for NICHD's response to this significant item regarding maternal-fetal medicine.

Item

Neurofibromatosis- Learning disabilities occur with high frequency in children with NF. The Committee recognizes that NF1 provides an opportunity to uncover a molecular basis for cognitive impairment and to identify a marker for brain dysfunction, and that research in understanding the cognitive deficits in NF1 patients possesses broad application to learning disabilities in the general population. NICHD is encouraged to expand its NF research portfolio, to coordinate its efforts with other Institutes engaged in NF research, and be prepared to report on its NF research portfolio at its fiscal year 2001 appropriations hearing. (p. 145)

Action taken or to be taken

Please refer to page NICHD-48 of this document for NICHD's response to this significant item regarding neurofibromatosis.

Item

Ob-Gyn Research- The Committee commends NICHD for providing grants to ob-gyn departments at 20 U.S. universities and hospitals to establish Women's Reproductive Health Research Career Development Centers. With the increased funds provided, the Committee encourages the Institute to expand the number of Women's Reproductive Health Research Career

Development Centers. At these centers, newly trained ob-gyn clinicians are provided training and support to assist in their pursuit of research careers to address problems in women's obstetric and gynecologic health, thereby improving the health of women and infants. (p. 145)

Action taken or to be taken

Please refer to page NICHD-54 of this document for NICHD's response to this significant item regarding the Women's Reproductive Health Research Career Development Centers.

Item

Pediatric Emergency Medicine- The Committee encourages NICHD to develop a research initiative on pediatric emergency medicine, including both prehospital and emergency care. To date, only minimal attention has been paid to addressing this costly and important aspect of children's health care. NICHD is encouraged to work closely with HRSA in the development of national educational programs and conferences to encourage and support research in emergency medical services for children. (p. 146)

Action taken or to be taken

Please refer to page NICHD-55 of this document for NICHD's response to this significant item regarding pediatric emergency medicine and the National Center for Medical Rehabilitation Research.

Item

Pediatric Kidney Disease- Despite scientific advances, kidney disease continues to be a major cause of illness and death among young people. NICHD is encouraged to enhance research on the understanding and treatment of congenital diseases and kidney malformations which lead to chronic renal failure and end-stage renal disease in children and adolescents, as well as the prevention and treatment of the adverse effects of chronic renal failure on neurologic and physical development in children. (p. 146)

Action taken or to be taken

Please refer to page NICHD-49 of this document for NICHD's response to this significant item regarding pediatric kidney disease.

Item

Pelvic Floor Dysfunction and Incontinence- The Committee commends the NICHD on the outstanding progress it has made in establishing a research portfolio in pelvic floor dysfunction and incontinence. It is the Committee's understanding that a workshop has been held on clinical terminology and that two requests for application will be issued this Spring to address translational and clinical research, specifically surgical interventions. The Committee urges

NICHD to continue at this level of commitment collaborating with NIDDK, NIA, and the Office of Research on Women's Health. (p. 146)

Action taken or to be taken

Please refer to page NICHD-49 of this document for NICHD's response to this significant item regarding pelvic floor dysfunction and incontinence.

Item

Primary Immunodeficiency Diseases- The Committee continues to be pleased with the comprehensive commitment that NICHD has demonstrated in addressing primary immunodeficiency diseases. The combination of peer-reviewed research funded in collaboration with the Jeffrey Modell Foundation and active participation in the Foundation's national education and awareness campaign show a serious commitment that should be replicated by other institutes. The Committee urges NICHD to remain committed to this collaboration. (p. 146)

Action taken or to be taken

Please refer to page NICHD-50 of this document for NICHD's response to this significant item regarding primary immune deficiency diseases.

Item

Small Grants- The Committee is pleased to learn that NICHD recently began promoting small grants as a way to attract new investigators to child development research. The Committee encourages the Institute to examine whether B/START small grant awards as used by other Institutes would encourage interest among its investigators. (p. 146)

Action taken or to be taken

The NICHD small grants (R03) program has been evaluated and it was determined that the B/START mechanism would offer no distinct advantages over the R03 for NICHD investigators. The R03 provides limited financial support (up to $50,000 per year for two years) for new biomedical and behavioral research projects relevant to the NICHD mission in population science; reproductive science; pregnancy and birth; human growth and nutrition; normal and atypical development; pediatric, adolescent and maternal HIV/AIDS; genetics and teratology; developmental biology; and medical rehabilitation research. Applications may be submitted on three dates per year.

The NICHD Small Grant mechanism is used primarily for new investigators beginning to establish a research program, for the collection of preliminary data which will serve as the basis for a competitive R01 application. Receipt of an R03 grant does not preclude an investigator next applying for an R01 as a new investigator. The Institute carefully monitors funding of new investigator R01 applications to ensure that a high level of grant support for promising

researchers is maintained and to ensure continued high quality research addressing the mission of the Institute.

With specific reference to the pool of new investigators of interest to the B/START program, i.e., behavioral scientists, evaluation of the NICHD Small Grants Program indicates that a substantial proportion of the applications received in this program are submitted by behavioral scientists. Specifically, almost one-third of the R03 applications are in the field of behavioral science, representing a larger proportion than submit applications for research project grants (R01). It appears, therefore, that although the NICHD Program is not limited to new behavioral scientists, it is attractive to that group. The addition of a program specifically designated 'B/START' would not enhance what is already available through the NICHD Small Grants Program.

Item

Vulvodynia- Hundreds of thousands of women suffer from vulvodynia, a painful and often debilitating disorder of the female reproductive system. Despite its prevalence, very little attention has been paid to the disorder by health professionals or researchers. In April of 1997, NIH convened an international symposium to exchange information and develop a research agenda. Since fiscal year 1998 the Committee has called on the NICHD to support research on the prevalence, causes and treatment of vulvodynia. The Committee is pleased NICHD recently published a request for applications in this area, but is concerned that additional steps to encourage researcher interest and the submission of fundable research proposals still have not been taken. The Committee continues to be very concerned with the slow pace of research progress made in this important area. The Committee has included additional funds in fiscal year 2001 for expanded research on vulvodynia. (p. 147)

Action taken or to be taken

Vulvodynia is considered a clinical condition with several different and poorly defined antecedents. There are many unexplored questions regarding this elusive pain syndrome. The goal is to build a substantive scientific knowledge base related to this debilitating condition and form a framework for assessing future research needs by stimulating clinically relevant research on promising biomedical, clinical or behavioral studies that will expand our knowledge of vulvodynia.

NICHD published a Request for Applications (RFA) that invited investigators to submit research grant applications to further our understanding of vulvodynia, and to stimulate and strengthen a multi- disciplinary approach to this complex, under- researched area of women's health. Three awards were made in response to the RFA. These proposals collectively comprise epidemiological, basic, and clinical research approaches to vulvodynia. One study proposes to survey women from the general population to estimate the age-specific prevalence of vulvodynia and determine the association of microorganisms and inflammatory agents in vaginal and vulvar specimens in women with vulvodynia. Another grant will examine the neurologic and immunologic factors associated with vulvodynia. A third project will integrate the prevalence, risk factors, and clinical correlates of vulvodynia with current treatment strategies such as dietary, cognitive–behavioral, topical steroids, and low-dose antidepressant therapies to

determine the validity of various treatments. In addition, NICHD funded a grant in response to the Program Announcement (PA) that focuses on the efficacy of established psychosocial intervention. These awards present a diverse, multi disciplinary approach to this pressing health concern.

NICHD is responding to a need to increase knowledge and understanding about vulvodynia and the biological processes that lead to its development and long-term sequelae. The workshop, subsequent RFA, and ongoing PA (PA-98-112) demonstrate our continued interest in this area and represent an expansion of ongoing research efforts.

Item

Childhood Birth Defects and Developmental Disorders- The Committee recognizes the importance of helping children suffering from birth defects and developmental disorders. Thousands of children each year suffer from birth defects and developmental disorders including cleft lip, cleft palate, missing limbs and other facial deformities from hemangiomas, hemifacial microsomia, microtia and aural atrresia, craniosynostosis. The Committee, therefore, urges the appropriate Institutes and Centers to expand and better coordinate their support of research into the causes, incidence, treatment and prevention of these and other children's congenital or developmental conditions and to consider developing a comprehensive action plan targeting these conditions. (p. 178)

Action taken or to be taken

In the United States, birth defects are the leading cause of infant mortality. While great process has been made in preventing infant deaths resulting from low-birth-weight, prematurity, respiratory distress syndrome and Sudden Infant Death Syndrome (SIDS), birth defects remain the leading cause of death in infants under one year in age, accounting for one in five infant deaths. It is estimated that more than 120,000 babies in the United States (about 4% of all live births) are born with major birth defects each year. Birth defects are involved in about half of all pediatric hospital admissions and, next to accidents, are the leading cause of death in children. Moreover, the estimated lifetime cost to the U.S. economy of children born each year with any of seventeen major birth defects is in the billions of dollars.

Considering the great impact of structural birth defects on public health, socioeconomics and family life, the NICHD is focusing its long-held interest in understanding the underlining basic mechanisms of normal development to develop a comprehensive program and strategy to support epidemiological, basic, translational and clinical research on human congenital malformations.

In recent years, the NICHD convened a series of workshops and reviewed the current knowledge regarding structural birth defects, identified the gaps in our understanding, and recommended and prioritized areas of future research. The first fruits of these efforts have been realized in two recent RFAs. The first of these RFAs, entitled " Genetic Susceptibility and Variability of Human Malformations," was funded in Spring 2000 by NICHD in collaboration with the National Institute of Dental and Craniofacial Research (NIDCR), National Institute of Environmental Health Sciences (NIEHS), and the Environmental Protection Agency (EPA). The 10 funded

studies on the genetic epidemiology of human malformations focus on the contributions of genetic and environmental factors to the etiology and distribution of disease within families and across populations. We believe these projects will lay the foundation for the development of future initiatives focusing on the molecular genetics and developmental biology of structural birth defects.

Other important recommendations of the earlier workshops were to foster interactions between basic and clinical investigators with common interest in birth defects and to establish and support interdisciplinary and integrated basic, clinical and translational research projects relating to the causes of developmental malformations. This approach was also subsequently encouraged by the President's Task Force on Children's Environmental Health and Safety Risks. These recommendations resulted in an RFA for program projects combining basic and clinical approaches to study the developmental biology and the molecular genetics of human malformations. The program project mechanism was selected because it is ideal for combining multiple basic and clinical component projects with a central theme and for fostering interactions and collaborations between basic and clinical scientists. Furthermore, the nucleus of multidisciplinary scientists in each program project will provide a fertile environment for cross-training basic and clinical investigators.

These projects, which will exploit the use of animal models to elucidate the basic molecular and genetic underpinnings of both normal development and the formation of malformations, will complement studies by clinical investigators on interrelated translational or clinical projects addressing a common central theme or research focus. This strategy is intended to maximize the opportunities for translating the basic findings of animal models into clinically relevant conditions in humans. This initiative, co-funded by the NICHD and the NIEHS, will fund up to six projects early in 2001. An important aspect of these interactions is the two-way flow of information from research endeavors. Findings from clinical studies should provide insight and direction to basic scientists studying developmental processes. Similarly, the translation of basic findings from the use of animal models to clinically relevant conditions will increase our understanding of human embryonic development and the formation of structural birth defects.

The NICHD has always put strong emphasis on the use of animal models as a means of elucidating the basic underlying mechanisms of normal development and the analysis of what happens when these processes go awry and lead to structural birth defects. The discovery of the conserved nature of genes and developmental process across species has provided credence for the use of such diverse animal models as *Drosophilia, Xenopus,* zebrafish, and the mouse to study developmental processes. Consequently, the increased understanding provided by work on model systems will also provide the basis for translational studies of human congenital defects. The NICHD will continue to emphasize the funding of such basic studies submitted as investigator-initiated proposals. But, through its active participation in a number of trans-NIH committees, the NICHD will also take a pro-active role in promoting the use of a variety of animal models. For example, the NICHD was the lead institute of an RFA co-sponsored by six other Institutes on Mouse Mutagenesis, which will create models for human congenital defects. A similar RFA sponsored by the NICHD and 15 other members of the Trans-NIH Zebrafish Coordinating Committee will produce mutants providing important information on the function of developmentally relevant genes. The use of such animal models is still our best chance for

defining the genetic networks and developmental processes associated with the birth of normal babies.

All of these projects are instrumental components of the NICHD Birth Defects Initiative. The further growth of this initiative is greatly encouraged by the designation of "Developmental Biology: Understanding Normal and Abnormal Development" as one of NICHD's Strategic Planning Areas. To encourage the growth of this initiative, investigators from the projects funded through these RFAs will be convened annually to discuss their findings, laying the groundwork for future collaborations and projects. These interactions will represent the beginning of a network of investigators from various disciplines with shared interest in birth defects. It is our hope that these efforts will grow to include the participation of other institutes and agencies for a truly national initiative focusing on birth defects.

Item

Children's Health and Safety - The Committee urges the Secretary to consider consulting with the National Academy of Sciences to provide an evaluation on childrens' health. This evaluation could assess the adequacy of currently available methods for assessing risks to children, identify scientific uncertainties associated with these methods, and develop a prioritized research agenda to reduce such uncertainties and improve risk assessment for children's health and safety. (p. 235)

Action taken or to be taken

The Secretary, HHS, co-chairs with the Environmental Protection Agency Administrator an interagency Task Force on Children's Environmental Health and Safety, established by executive order. The major focus of these activities has been on asthma, cancer, injury, and developmental disorders. With regard to the issue of evaluating children's health and risks to children, the Task Force developed and initiated a National Longitudinal Cohort Study of Children's Health and Development. This study was subsequently endorsed by Congress in the Children's Health Act (P.L. 106-310), which directed the NICHD to take the lead role in a multiagency effort to design and conduct this study. These efforts are currently in progress, and the resulting study should reduce uncertainties about methods of assessing risks to children, as well as improve methods to measure children's health and safety.

FY 2001 Conference Report Language (H. Rpt. 106-1033)

Item

Children's Health - The conferees are supportive of plans to conduct a national longitudinal study of environmental influences on children's health. The Director of NICHD is urged to establish a consortium of representatives from appropriate Federal agencies, including CDC, EPA and other NIH Institutes to plan and initiate pilot studies that will provide the information necessary to develop and implement the full national longitudinal study. To this end, the conferees have provided funds to support this initiative and look forward to learning of the progress made during the fiscal year 2002 appropriations hearing. (p.137)

Action taken or to be taken

NICHD is leading the process for planning the National Longitudinal Study. The Institute has staff dedicated to the Study and has worked to establish meaningful collaborations with both CDC and EPA and many other federal partners.

NICHD has made substantial progress in establishing cooperative working relationships with other NIH Institutes and Centers and many federal agencies. An interagency coordinating committee comprised of staff from NICHD, the DHHS Office of the Secretary, the Centers for Disease Control and Prevention and the U.S. Environmental Protection Agency has carried out a number of essential planning steps, including an operational guide to steer the planning process and the development of core hypotheses. In addition, the committee has devised a structure for planning and implementing the Study that provides for innovative public-private and inter-agency partnerships throughout the process. The consortium of Federal agencies working on the study is formalized by Memorandum of Understanding.

The NICHD has begun working to establish a group of representatives from NIH Institutes and Centers to coordinate research efforts and provide advice. Support from a large number of Institutes and Centers has been strong. During the next fiscal year, these relationships will be strengthened as more opportunities for collaboration and involvement in the Study arise.
An open Consultation for the Study in December 2000 involved over 250 federal and non-federal scientists and was successful in identifying detailed considerations for planning the Study and numerous collaborators for conducting the Study. In February, 2001, the interagency coordinating committee convened a meeting of all interested Federal agencies to formalize their involvement in the Study planning process. Interested Federal staff were able to express interest in joining a working group to focus on specific environmental exposures, disease outcomes, research ethics, genomics, and other core areas. These working groups will be formally established in fiscal year 2001 with the addition of many non-government representatives from advocacy organizations, parent groups, environmental groups, industry, academic institutions, and other interested stakeholder groups. Overall, it is expected that 100 to 200 interested individuals will be involved in some way in the planning of the Study.

A chartered Federal Advisory Committee will be established this year to provide for formal external input and review of all aspects of the planning and implementation process. A website dedicated to the Study was established this year and is expected to provide for state of the art communications among stakeholders.

During fiscal year 2001, NICHD worked with CDC and EPA to plan some early pilot research of key epidemiological techniques. It is expected that NICHD will fund some of this research this year with an increased role in funding it next year as more pilot testing will be needed. Pilot testing for fiscal year 2002 will continue to focus on studies to optimize exposure measurement techniques through a systematic evaluation of all applicable exposure methodologies; development of bio-markers for assessment of adverse health outcomes from exposure to environmental agents; methods for collection and isolation of genetic material applicable to a community based longitudinal study; evaluation and piloting methods for sample selection, recruitment and retention; identification of emerging and innovative technologies for measurements; and data management applicable to a large cohort study.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2000 Amount Authorized	2001 Estimate	2002 Amount Authorized	2002 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite	$951,340,000	Indefinite	$1,065,836,000
Health and Human Development	Section 448	42§285g	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	42§288	a/	27,566,000	b/	30,814,000
Total, Budget Authority				978,906,000		1,096,650,000

a/ Funding provided under the Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 2001 (P.L. 106-554).

b/ Reauthorizing legislation will be submitted.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Appropriation History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1993	$545,238,000	$534,094,000	$534,094,000	$527,789,000
1994	542,357,000	555,195,000	555,195,000	554,881,000 2/
1995 3/	516,736,000	513,159,000	513,159,000	512,852,000 4/
Rescission				(687,000)
1996	526,177,000 3/	595,162,000	518,585,000 3/	595,162,000
Rescission				(615,000)
1997	543,441,000 3/	631,989,000	554,251,000 3/	631,703,000
Rescission				(338,000)
1998	582,032,000 3/	666,682,000	676,870,000	674,766,000
1999	654,248,000 4/5/	728,817,000	748,482,000	750,982,000
Rescission				(497,000)
2000	694,114,000 3/	817,470,000	848,044,000	862,884,000
Rescission				(4,593,000)
2001	810,501,000 3/	984,300,000	986,069,000	976,455,000
Rescission				(486,000)
2002	1,096,650,000			

1/ Reflects enacted supplementals, rescissions and reappropriations.
2/ Excludes enacted administrative reduction of $6,305,000.
3/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research.
4/ Excludes enacted administrative reduction of $557,000.
5/ Reflects a decrease of $468,000 for the budget amendment for bioterrorism.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Detail of Full-Time Equivalent Employment (FTEs)

OFFICE/DIVISION	FY 2000 Actual	FY 2001 Estimate	FY 2002 Estimate
Office of the Director	20	19	19
Office of Administrative Mgmt.	63	63	65
Office of Science Policy, Analysis and Communication	25	25	25
Center for Population Research	33	33	34
Center for Research for Mothers and Children	45	45	46
National Center for Medical Rehabilitation Research	5	6	7
Division of Scientific Review	18	19	20
Division of Epidemiology, Statistics, and Prevention Research	22	23	24
Division of Intramural Research	311	326	340
Total, NICHD	542	559	580
FTEs supported by funds from Cooperative Research and Development Agreements	(3)	(4)	(4)

FISCAL YEAR	Average GM/GS Grade
1998	11.1
1999	11.2
2000	11.1
2001	11.1
2002	11.1

NATIONAL INSTITUTES OF HEALTH
National Institute of Child Health and Human Development
Program Administration

Detail of Positions

GRADE	FY 2000 Actual	FY 2001 Estimate	FY 2002 Estimate
ES-6	0	0	0
ES-5	0	0	0
ES-4	3	3	3
ES-3	0	0	0
ES-2	1	1	1
ES-1	0	0	0
Subtotal	4	4	4
Total - ES Salary	$511,864	$532,300	$553,400
GM/GS-15	49	48	49
GM/GS-14	74	70	72
GM/GS-13	41	42	43
GS-12	40	41	44
GS-11	30	32	35
GS-10	2	2	2
GS-9	33	36	37
GS-8	41	41	41
GS-7	31	35	35
GS-6	21	17	17
GS-5	10	9	11
GS-4	3	5	5
GS-3	1	2	2
GS-1	0	0	0
Subtotal	376	380	393
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	0	0	0
Director Grade	9	7	7
Senior Grade	9	9	9
Full Grade	5	5	5
Senior Assistant Grade	1	2	2
Assistant Grade	0	0	0
Co-Step	0	0	0
Subtotal	24	23	23
Ungraded	154	165	174
Total permanent positions	405	407	412
Total positions, end of year	558	572	594
Total full-time equivalent (FTE) employment,end of year	542	559	580
Average ES level	ES-4	ES-4	ES-4
Average ES salary	$127,966	$133,100	$138,400
Average GM/GS grade	11.1	11.1	11.1
Average GM/GS salary	$62,009	$64,500	$67,500

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

New Positions Requested

	FY 2002		
	Grade	Number	Annual Salary
Research Fellow	Ungraded	4	$80,000
Clinical Fellow	Ungraded	5	85,000
Health Scientistist Administrator	GS-15	1	100,000
Health Scientistist Administrator	GS-14	2	82,000
Senior Lab. Technician	GS-12	2	58,200
Lab. Technician	GS-11	2	48,200
Grants Financial Analyst	GS-12	1	58,200
Lab. Technician	GS-9	1	40,300
Program Analyst	GS-12	1	58,200
Public Information Specialist	GS -13	1	67,400
Secretary	GS-5	1	26,900
Total Requested		21	